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Review Article

Gut microbita and probiotics in anti-cancer therapy: A promising future

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ABSTRACT

Cancer is a significant wellbeing trouble with multifactorial pathology, and is the second conspicuous reason for worldwide deaths. Regardless of all ongoing advancements in the clinical administrations, protection from standard medications and antagonistic impacts actually speak to a significant reason for treatment failure and helpful disappointment in cancer. Researchers are trying to look forward for inventive treatments and prophylaxis in cancer therapy. The statistics shows that cancer threats are indubitably influenced by immunological condition and genetic factors of the organism. There are growing evidences about the responses of chemo as well as immunotherapeutic medications by regulating the efficacy or toxicity by gut bacteria as well as preserving host's health and to maintain balanced homeostasis. A number of metabolites as well as bio products which are necessary to safeguard host's and gut's homeostasis are produced by Gut resident bacteria. Furthermore, intratumor bacteria can possibly regulate chemotherapy reaction. Microbiota compositions are specifically affected by anticancer therapy. Importantly, gut microbiota effectively relate with host by directly modulating the immune system or the gut epithelium. Several gut populating bacteria, named probiotics, were recognized as defensive against the growth of cancer cell. With their known ability to preserve gut homeostasis, probiotics are presently studied to battle dysbiosis in patients who are undergoing chemotherapy as well as radiotherapy. The profoundly critical examinations, revealing the tight connection among gut microbiota with tumorigenesis, along with gut microbiota, probiotics and anti-cancer treatment, are described in this review.

Keywords: Microbiota, Probiotics, Cancer, Anti-cancer therapy

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INTRODUCTION

Cancer is the primary source of death rates which is related with tremendous economic and social burdens.[1] Cancer prevalence is growing due to the failure in demographics and cancer associated lifestyles such as smoking, radiation exposure, diets and physical inactivity in most of developing nations.[2] Increased exposure to carcinogens is a subsidising factor. Parallel to several other multifarious diseases, cancer susceptibility and development are mostly influenced by the interactions of gene–environment. One side, there are many significant progression on understanding the genetics and the cellular biological mechanisms which lies beneath the carcinogenesis.[3]

Recent years, many evidences sharpen towards the crucial role of commensal bacteria colonizing body surfaces as significant factors of well-being or pathologic illnesses, especially cancer.[4] The human intestine is home to about 3.8×1013 microorganisms with weight of almost 1.8kg, named as gut microbiota, which maintain host physiology and health by employing fundamental functions, from metabolic to immune modulatory properties.[5] Gut microbiota is the diverse population of commensal microorganisms, predominantly bacteria, it also consist of viruses, fungi, and archaea, colonizing the intestinal tract, mainly the large intestine which are mostly exposed, at high doses, all through the whole lifecycle.[6] The gut microbiota plays out various significant functions, including vitamin production, utilization of dietary compounds, protection against the development and fundamental invasion of gut pathogens.[7] Eubiosis is defined as an equilibrium with the host by microbiota. Different diseases, like cancer can change this balance which may result in alteration of the microbial ecology.[8] Microbial dysbiosis not only affects the therapeutic outcome but also contributes to pathogenesis and progression of cancer which is associated to the capability of microbes to metabolize medications and xenobiotics. It also modifies host immune and inflammation responses.[9] In gut microbiome, the entire genome of the host's gut microbiota, encodes for additional qualities than the human genome in 100-folds.[10] During the former decade, the initiation of metagenomics, uniting next-generation sequencing (NGS) along with computational investigation of 16 SrRNA amplicons, enable to distinguish both diversity and copiousness of the gut microbiome. Progresses in metagenomics studies, along with the developments in metabolomics and transcriptomics, defines the influence of specific bacterial species on host's health.[11] That denotes a period towards, from descriptive composition analyses, to functional studies of micrrobiomes. Currently these are helping to recognize the true effect of the microbiome architecture on human health.[12] However these entiire pathologies are associated with the gut microbiome, mostly commonly considered is tumorigenesis. These connections were observed between both local gastro-intestinal cancers and other distal tumors.[13] Metabolomics and metagenomics trials emphasizes the roles of microbiome of gastro-intestinal tract in prevention of cancer, tumorigenesis as well as anti-cancer therapy.[14] The fact is that these gut microbiome can either function as tumor-suppressive or oncogenic.[15] While this relationship is observed since long back, it is only partly categorized. All these recent knowledge highlights the complexity and bi directionality of the link existing between cancer and microbiome. As a major concern, cancer advancement can alter the microbiome and, in turn, microbiome variations can affect progression of cancer.[16]

Cancer drugs are precisely intended to target malignancies, but also toxic for normal cells, with various side effects, some are even life-threatening. The adverse effects need a reduction of the dosage or the alteration of drug regimen for the treatment tolerable and effective to the patient. Another major issue associated with anticancer therapy is drug resistance, that can causes failure of chemotherapeutic treatment.[17] This failure can be halfway clarified by have hereditary or genetic aspects, even though other aspects are also involved. In current years, efforts mainly aimed to improve the therapeutic outcomes specifically towards the cancerous cells and very fewer host related toxicity. In this scenario, immunotherapy has given a change in oncology, with drugs to specifically targeting the immune cells other than cancer cells, intended at stimulating the immune response against cancer activity.[18] Both in chemotherapy as well as immunotherapy, resident microorganisms have the ability to interfere directly or indirectly with host-targeted therapy by three main clinical effects: (i) enable drug efficacy, (ii) retract and conciliate anticancer effects, and (iii) facilitate toxicity. Most deliberate fact is that anticancer therapies along with cancer itself can possibly alter the microbiota profile in cancer patients.[19]In recent years interactions within anticancer drugs and microbiota have drawn greater interest among researchers. Therefore interventions are designed at influencing microbiota to enhance efficacy of drug and lessen side effects.

Based on this, it has been projected the simultaneous administration of probiotics, synbiotics, prebiotics, antibiotics or postbiotics along with cancer treatment to rebalance the gut microbiota.[20] Probiotics are best characterized as a preparation of, or a product with viable, well-

defined micro-organisms in adequate numbers that have the potential to modify microflora either by implantation or colonization, in a host compartment and provide favorable effects on the host.[21] Probiotics is defined as a diverse group of bacterial organisms. These organisms exert influence by changing the micro biota, bio product secretion, cell surface molecule expression, and host immune system. Probiotic mechanisms of action are Antibacterial activity, improvement of mucosal barrier function and immunomodulation.[22] The term prebiotic is referred as a group of non-digestible oligosaccharide which are selectively fermentable and produces particular changes in composition as well as activity of the gastrointestinal microflora, conversing health benefits.[21] Both probiotics and prebiotics may signify a way to re-establish commensal microorganisms which are blocked by anticancer therapy and a healthy gut environment. They are combined to form synbiotics. Synbiotics are formulations of prebiotic compounds selectively errand the progress of probiotic organisms to produce synergistic effect.[23] Additionally, postbiotics use, that is nonviable microbial products having biological activities[24], can also parodist the probiotic's beneficial effects. Postbiotics, such as short-chain fatty acids acetate, butyrate and propionate, can offer benefits to the hosts which are commonly secured by healthy and composed microbiota.

Better interpreting the relationship between immunotherapy, chemotherapy and microbiota may uncover new therapeutic targets along with innovative integrated approaches to upsurge the clinical treatment of cancer patients. This review focuses to understand the solid relationship between tumorigenesis and gut microbiota in chemotherapy as well as immunotherapy. Additionally, the significance of probiotics with anti-cancer therapy is also be discussed.

GUT MICROBIOTA AS A TUMOR-SUPPRESSOR

Depending on the composition, gut microbial population can affect pathological processes for example initiation and development of cancer, either positively or negatively. Few of microorganism-derived molecules have activity against tumor cells.Microbial-derived short chain fatty acids shows an anti-cancer effect. Gut bacterial propionate and butyrate have the ability to inhibit tumor cells histone deacetylases of the host with an overall anti-cancer effect in lymphoma and colorectal cancer(CRC).[25,26] GI bacteria metabolize dietary elements into presumed tumor-suppressive metabolites, which includes daidzein in soy-based products is converted to equol, as an antioxidant; glucosinolates in cruciferous vegetables are converted to sulforaphane and other isothiocyantes that function as HDAC inhibitors with anti-inflammatory effects; ellagic acid in certain berries is metabolized to urolithins which alter estrogens and inhibit COX-2 and inflammation.[27,28] By setting of an indirect immune-mediated response against the progression of tumor, several probiotics' derived metabolites and molecules are capable to adjust the immune system of the host. The extensively examined bacterial lipopolysaccharide (LPS), outer membrane component in gram-negative bacteria, stimulates the host's cell surface receptor toll-like receptor 4 (TLR4) by activating immune T cell-mediated response against cancer cells.[29] Currently monophosphoryl lipid A (MPL) a component of Salmonella enterica was used as an adjuvant in the antibody plan against hostile to cervical carcinoma.[30] Additionally, bacterial derived group B vitamin, pyridoxine, stimulate host's anti tumoral immune surveillance.[31] Various commensal microorganisms assume a probiotic function to present medical advantages, by securing against gut dysbiosis or upgrades host's resistant safeguard mechanisms.[32] The co-administration of such probiotics alongwith the intestinal antibiotic like rifaximin, shows a clear anti- inflammatory activity in animal model studies in inflammatory bowel disease.[33] Moreover, many probiotics discloses potential antineoplastic activity.For example to restrain tumor development probiotics or probiotics-derived metabolites are administered to mice. Ferricrome metabolite from Lactobacillus casei secretion, can elicit apoptosis in tumor cells by the direct activation of JNK pathway.[34] Similarly several studies reported Lactobacilli can possibly stimulate host's immune cells for example, NK cells or TH1 response or dendritic cells (DC), that can eliminate cancerous or precancerous cells.[35,36]

GUT MICROBIOTA AND ANTI-CANCER THERAPY

Anti-cancer therapies are intended with the objective of being successful in the termination of the targeted malignancy. All these current anti-cancer therapies are noxious towards normal cells, combined with side effects, certain can even compromise the overall patient survival.[37] Moreover, tumors are even intrinsically complex: since they aim to accumulate mutations, it develop and adjust with the facilitating organism. In fact, a cancer involves the mutations within genes having important processes, such as DNA repair, DNA duplication and oxidative stress response. These accumulation causes the conversion of a typical cell into a malignant one.[38] The initiation and the development of a tumor can be observed as a combined impairment of basic cellular processes,

implying that from one unique cancer cell may derive a molecularly diverse large tumor with multiple cancer clone cells.[39] This heterogeneity derives from intrinsic tumor cellular genomic variability, reaching from micro satellite instability (DNA mismatch repair system impairment) to chromosomal instability (segregation errors during cell mitosis).[40,41] These genetic mechanisms might be combined with epigenetics, transcriptional and post-transcriptional intracellular changes, finally becomes reasons for growing tumor complexity.[42] In fact this intra-tumoral variability is closely connected with the progress of resistance to treatment, considered the first and major reason for failure of the current cancer therapy. Under such circumstances, incorporated treatments and individualized approaches, in light of particular genetic features of the malignancy, are in constant advancement to eradicate these condition.[43] Developing malignant cells are not only exposed to their intrinsic heterogeneity, furthermore they are also identified and removed by the immune system of the host. Tumor cells because of their genetic or hereditary instability, frequently evolve new approaches to escape from insusceptible immune surveillance and multiply within the host.[44] Novel anti-cancer approach called targeted immunotherapy, providing the double role of enhancing the host anti-tumor immune response, and assisting with hitting cancer resistance and relapse mechanisms is now effective with radiotherapy and chemotherapy.[45,46]

Modulating gut microbiome can profoundly influence the anti-cancer therapy outcomes. Even though, radiotherapy, chemotherapy and immunotherapy treatments can all modify patients' microbiome, the microbiome can also deeply affect patient's response to such therapies.[47] Thus it is necessary to identify which are the factors responsible to influence the gut microbiome and to find novel approaches to manipulate the gut microbiome, with the ultimate aim to improve patients therapeutic outcome and quality of life. Specifically, interventions on microbiome could be crucial to ameliorate anti-cancer treatment-associated toxicity and to improve efficacy of anti-cancer therapy.[48,49] Several studies has been done with microorganisms in order to evaluate the microbiome effect in cancer therapy. As an effort to cure cancer, two heat-inactivated microbes (Streptococci) are intratumorally injected in humans for the first time in 1890s.[50,51] Later, following the resection in bladder tumor, Mycobacterium bovis was effectively injected into bladder. It has been detected that the bacteria, by inducing a local immune response, reduced the relapse of the tumor.[52] These observations opened the way for many trials, based on the usage of gut bacterial attenuated strains in anti-cancer therapy.[53] For instance, itwas witnessed that Mycobacterium obuense intradermal injection stimulates antitumoral immune response by acting on antigen presenting cells (APCs) and cytotoxic T cells of host in melanoma as well as in pancreatic ductal carcinoma.[54,55] Further diverse refractory solid tumor observations with genetically modified Salmonellatyphimurium shows weakened microorganisms infused legitimately into the tumor mass can invigorate against tumoral resistant reaction and to have a direct cytotoxic impact on the tumor cells, because of their ability of colonizing tumors.[56,57]

Latest preclinical and few clinical studies concentrating on various cancer types, evidently support that gut bacteria plays a important part in modulation of host response to anti-tumor drugs, mainly with chemotherapy and immunotherapy.[58] It is suggested that anticancer therapy responses of gut microbes is by tempering drug efficacy, eliminating the anticancer outcome, and intervening toxicity. Although the fact that the components are not surely known, certain of studies depicts it as Translocation, Immunomodulation, Metabolism, Enzymatic degradation and Reduced diversity which comes under "TIMER" framework mechanism.[59] while these outcomes are promising, many clinical trials are presently continuing in order to enhance the clinical outcomes of patients, given bacteria-related toxicity, generally correlated to their long half-life.

EFFECT OF GUT MICROBIOTA IN CHEMOTHERAPY, IMMUNOTHERAPY AND RADIOTHERAPY

The microbiota, once influenced by dysbiosis, may intensely influence cancer pathogenesis as well as its therapeutic outcome. In precise, the regulation of the therapeutic outcome is strongly linked with the capability of the gut microbiota to metabolize anti-tumoral compounds and to modulate immune response and inflammation pathways of the host.[60] These effects elucidate the association of the patient's microbiome composition in affecting the efficacy of chemotherapy, immunotherapy and radiotherapy.[61]

CHEMOTHERAPY

Gut microbiota and intratumor bacteria could modify chemotherapy efficacy and arbitrate its toxic effects. Several studies were evident that the presence of particular bacteria in tumor tissues and its capacity to modulate chemotherapeutic medication response.[62,63] Gut microbiota associated on chemotherapy efficacy by several mechanisms, like xenometabolism, altered community structure and immune interactions.[64] The gut microbiome can metabolize some xenobiotics mainly anticancer drugs directly. This microbe-mediated

xenometabolism could be associated to rise the chemotherapeutic component toxicity, leading to lessening in treatment efficacy.[65,66] The tumor-retardation effects of oxaliplatin (platinum chemotherapeutic) rely upon microbiota. In germ-free mice, oxaliplatin efficacy was weakened because of decreased intratumoral ROS generation.[67] Furthermore, when people undergo antibiotic treatment, the enlistment of immune cells essential for arbitrating tumor regression was reduced, and their pro inflammatory potential were also decreased. This results suggests microbiota mediated immune modulatory effects in response to chemotherapeutic compounds.The most expected instance of toxicity related with 5-fluorouracil (5-FU) sorivudine bi-therapy and incuded Bacteroidesspp was reported in Japan. In fact, Bacteroidesspecies, foremost members of intestinal microbiota, which inhibits 5-FU degradation by its high action of sorivudine alteration to an intermediate (BVU). This will results the accumulation in the blood and leads to higher toxicity.[68,69] Studies in mice revealed5-FU instigated intestinal dysbiosisis increased with Staphylococcus and Clostridium species and also reduced by Lactobacillus, Enterobacteriaceae and Bacteroides.[70] Similarly, doxorubicin or 5-FU or irinotecan induced intestinal mucositis, are linked with dysbiosis in the microbiota of the gut and oral cavity.[71,72] It was concluded that a reduction in microbiota diversity, richness, and dysbiosis, could worsen side effect inmurine models in cancer patients and in cancer.[73-75] This results in recent studies showed that microbiome modulation by nourishment or probiotic supplementation can decrease the chemotherapy toxicity and following side effects in mice andhumans.[76-78]

In addition to this, gut microbiota also have greater impact on chemotherapy efficacy in pre-clinical stuidies of different subcutaneous solid tumors like melanoma, lung cancer, colon and sarcoma.[79,80] An alkylating agent cyclophosphamide (CTX)is used for the management of solid tumors and lymphomas are identified to modulate the tumor immune microenvironment by decreasing regulatory T cells (Tregs) and increasing Th1 and Th17 cells.[81,82]Dysbiosis due to antibiotic therapy has been negatively correlated with the efficacy of CTX. Enterococcus hirae was recognized to move from the gut to lymph nodes and to persuade Th1 and pathogenic Th17 reactions that are needed for the anti-tumor action of CTX. Barnesiella intestinihominis, amassed in the colon, increases systemic level of Th1 and Tc1, polyfunctional CD8+ cytotoxic T-cells subpopulation, linked with a rise of IFN-y-producing ?d tumor infiltrating-lymphocytes (TILs) that can also upsurge the anti-tumor effect of CTX.[83] Along with active metabolic activities intratumoral bacteria can directly modulate chemotherapy efficacy.In vitro studies revealed a reduced anti-tumoral efficacy in Mycoplasma hyorhinis-infected cells by pyrimidine nucleoside analogues. In fact, mycoplasma athymidine phosphorylase can directly degrade these anticancer drugs in tumor cell.[84] Furthermore, it has been shown that cytidinedeaminase-harboring bacteria, like gamma proteobacteria, are involved in the gemcitabine (GTB) and OXA resistance of mice colorectal tumors and also in human pancreatic ductal adenocarcinoma.[85-87] Altogether these facts recommends the gut microbiota appears to be a crucial biomarker for improving the effect of chemotherapy regimens.Additional clinical studies should be done to assess these innovative markers.

IMMUNOTHERAPY

The significant action of gut microbiota on efficacy of immunotherapy was shown in various studies which emphasized the association immune host response and bacteria in anti-tumor activity.[67] The efficacy of anti-tumor CD8+ T cells adoptive exchange in a melanoma murine model was improved after the full body irradiation of mice by the translocation of gut bacteria into mesenteric lymphnodes. The release of microbial lipopolysaccharide (LPS) brought by irradiation stimulated innate immune response by TLR4 pathway activation and then enhanced anti-tumor CD8+ T cells, whereas antibiotic therapy was linked with a reduction of anti-tumor response.[88] This effect of the gutmicrobial composition on anti-tumor T cells has been newly identified in B-cell lymphoma, and in cervix and lung tumor mice models.[89] A study conducted by Iida et al identified that antibiotic management reduced the efficacy of the anti-IL-10/CpGoligodeoxynucleotides (ODN) immunotherapy in MC38 B16 melanoma and colon carcinoma murine models. This could be due to a reduction of the gut microbiota, promoting thepro-inflammatory cytokines-producing monocyte decline in tumor.[67] Currently, the influence of the gut microbiota on immune checkpoint inhibitor (ICI) therapy efficacy as well as toxicity was alsostudied.[90-97] Even the reasons were not clear, these studies confirm the crucial part of gut microbiota on modulation of remote lymphoid and myeloid cells.[93,98,99] The first study on ICI concentrated on sarcoma, colon carcinoma and melanoma murine models. One of the study on ICI focused sarcoma, colon carcinoma and melanoma murine models revealed that mice undergoing antibiotic-therapy or GF mice do not have the ability to react towards the cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor antibody compared to SPF mice.[90,91] Another study underlined that the response to anti-programmeddeath-ligand1(PD-L1) was dependent on the gut microbiota composition and predominantly that Bifidobacterium spp. was

associated to effective response toanti-PD-L1.[90] ICI therapy efficacy by an growth of IFN-? +CD8+T-cells in tumor was restored by administration of Bifidobacteriumspp. In solid epithelial tumors, microbiota composition could be able to predict the eminence of responder as well as non-responder patients towards the anti-programmed cell death 1 (PD-1)/PD-L1 therapy.[93-96,100] A recent study was done to exhibit the function of Microbiota on ICI efficacy in melanoma patients, highlighted that antibiotics usage in the initial 30 days of ICI treatment can shorten the progression free survival compared to patients without antibiotic therapy.[101] Faecalibacterium showed relevant positive relationship with progression-free survival, whereas Bacteroidales increases the relapse risk. Patients having greater plenitude of Faecalibacterium through the treatment baseline had previous anticancer immune responses, as well as greater number of cytotoxic CD8 + T cells were identified to have infiltrated the tumor bed.[102,103] Similarly, a study analyzed 38 fecal samples from metastatic melanoma patients undergoing anti-PD1 treatment and identified that Bifidobacteriumlongum, Enterococcus faecium, and Collinsellaaerofaciens contributed to a better prognosis.With an R patient fecalmicrobiota exchange in germ-free mice shows improved control oftumor and responded more effectively to anti-PD-L1.[104] These encouraging results powerfully support the addition of microbial aiming in anti-tumor immunotherapy strategies to improve their efficacy. For a better knowledge of the underlying molecular mechanisms, more humanized animal models will be needed.

RADIOTHERAPY

Radiotherapy is the commonly used treatments for solid cancers based on its genotoxic effect on tumor cells. By an indirect energy transfer ionizing radiation produces DNA destruction directly through the reactive oxygen or nitrogen species production.[105,106] Moreover, radiotherapy could induce immunogenic death of the tumor cell by local irradiation, local and systemic inflammation and immunity.[107] Radiotherapy is even responsible for the stimulating the innate immune system. Barker et al.[108] highlighted the trigged release of inflammatory cytokines like IL-1 and TNF-a and immune cell recruitment after the therapy. However, after radiation therapy the tumor response remains very complex due to significant differences from patient to patient with variable oncologic outcomes. The reason of this complexity remains uncertain but latest observations shows that respose to tumor might be greatly affected by gut microbiota. The main function of intestinal microbiota in radio sensitivity is a novel concept but with only few original studies for convincing results.[105]Recent preclinical studies on mouse models were aimed to find the relationship among gut microbiota and radio resistance. Cui et al.[109] studied the effect of radiotherapy on circadian rhythm with the composition of the microbiota. And it was concluded that mice having typical 12-h dark/12-h light cycles showed improved existence rate than mice with different cycles. This finding is highly connected to modifications in gut bacterial communities that can even be a cause of the radio resistance mechanisms. They also explains a association between intestinal bacteria and radio-sensitivity with mouse model treated by antibiotics. The enteric bacterial composition of the antibiotic treated mice was specifically diverse from the control group and the survival rate of mice undergoing antibiotic therapy was specifically greater after irradiation.[110] Alternative assumption concerns the association among radioresistance and autophagy regulation.[111] Digomann et al.[112] described the expression level of certain proteins in autophagy was connected with the patients clinical prognosis mainly in head and neck squamous cell carcinoma undergoing radio chemotherapy[113] Gut microbiota may also affect radio-induced toxicity. Radiotherapy side effects including genomic instability, bystander impact on adjacent cells, and systemic radio-associated immune and inflammatory reactivity[114] can change quality of life and are vital aspect of the treatment choice. In a clinical study Ferreira et al.[115] showed the close relation between the composition of gut microbiota and radiation enteropathy. Patients undergoing radiation enteropathy there is a significant increase in Clostridium, Roseburia and Phascolarctobacterium. Also an inverse correlation between Propioni bacterium and Rectal Roseburia at the rate of IL-15. which was reduced radiation enteropathy.[116] After pelvic radiation, radiation-induced bowel toxicity was proven and is currently recognized that ionizing radiation was the cause for microbiota dysbiosis.[115-118] Another clinical study showed a significant variation of Firmicutes/ Bacteroidetes ratio in patients after receiving pelvic radiation who had developed diarrhea.[119] Totally these studies conclude that gut microbial dysbiosis might be a beneficial biological marker to predict and avoid radiation enteropathy or other complications.[119-121] Gastro-intestinal tract function is enhanced by faecal transplantation in irradiated mice and it also protect against radiation-induced death.[110] Moreover, in an animal model it was found that radiation s from neoadjuvants might alter the phenotypic virulence of Pseudomonasaeruginosa, leading to improved activity of collagenase, junction disruption after the epithelial cell death and whole monolayer destruction.[122] Another studies revealed that intestinal microbiota have a significant effect on total body irradiation. Irradiation drives less endothelial cells of the intestinal mucosa into

apoptosis and actuates fewer lymphocyte infiltration in germ-free mice than in conventional mice.[123] In conclusion, intestinal microbiota have a vital part in the variation of systemic immune response with radiosensitivity as well as radio-induced toxicity modulation.[124] However, the straight effect of gut microbiota on radiotherapy efficacy was not certainly demonstrated yet.[121] Additionally preclinical and clinical trilas are necessary to find the microbial populaces engaged in radioresistance.

USE OF PROBIOTICS IN CANCER THERAPY

Several preclinical studies as well as clinical trials were done to evaluate the action of probiotics in reducing the risk and the severity of anti-cancer treatments related-toxicity, especially diarrhoea and mucositis.[125,126] The goal of probiotic administration to cancer patients is to re-populate the gut microbiota of the compromised patients, to re-establish the functionality of the commensal bacteria which is depleted after the treatments.[127] A multicentered phase III randomized controlled study was conducted with 223 uterine cervix carcinoma patients and revealed that combining management with heat-killed Lactobacillus casei strains (LC9018) and radiation improves tumor regression by induction of immune response against malignant cells.[128] Indeed, gut microbiota also regulate and repair the irradiation-induced damages.[129] A study conducted by Ciorba et al.[130] showed probiotic strain Lactobacillus rhamnosus GG (LGG) safeguard the mouse from intestinal mucosa irradiation-related toxicity by the repositioning the cyclooxygenase 2-expressing cells. Even though probiotics are mostly considered to be safe, the main aim of administering them toimmune compromised cancer patients are the potential risk of opportunistic infection development and the transfer of antibiotics resistance.[131,132] Multiple trials with probiotic administration especially with Lactobacillus species showed beneficial effects on ameliorating diarrhea and gastrointestinal damages after chemotherapy and/or radiation therapy. This re-establishes a healthier intestinal microbiota composition in pelvic malignancy.[133-135] Recently, many studies aimed to investigate the therapeutic outcome of manipulating gut microbiota in cancer patients. A mouse model of cutaneous melanoma Sivan et al stated that, Bifidobacterium are related with moderate tumor growth and favorable responses to anti-PD-L1 treatment. In this study, oral probiotics having Bifidobacterium was administered to mice harbouring unfavourable gut microbiota improves the anti-tumor efficacy of PD-L1 blockade and closely eliminated the tumor growth.[136] A study by Wang et al. revealed that providing mice with probiotic strain Lactobacillus reuteri blocked the development and advancement of ICI treatment-linked colitis in melanoma tumor-bearing mice not by affecting the antitumor effect of the immunotherapy.[137]Viaud et al. conducted a study on tumor-bearing mice concentrated on the key role by the gut microbiota on CTX therapy and found a destruction of gut mucosal integrity connected with dysbiosis in CTX-treated animals. They observed, supplementation with Lactobacillus johnsonii and Enterococcus hirae in antibiotic-treated mice helped to restore CTX-mediated Th17 cell conversion.[138] The interaction between probiotic administration, variation of gut microbiota composition, and control of intestinal immune-functions was assessed in cancer patients undergoing colorectal resection by administration probiotic species such as Bifidobacteriumlongum (BB536) and Lactobacillus johnsonii (La1) founded that La1 had the ability to stick to colonic mucosa, thus decreasing concentration of the gut pathogens and to modulate the local immunity.[139] Another randomized clinical trial showed a substantial dropping in postoperative infection rates in CRC patients with perioperative administration of a mixture of prebiotics and probiotics.[140] In 2017, the randomized administration of Bifidobacteriumlactis and Lactobacillusacidophilus to CRC patients, may change the tumor tissue patterns from its baseline, with treatment benefits in CRC by manipulating the gut microbiota.[141] Beyond the beneficial effects observed, more trials or studies are further required to validate both the efficacy and the safety probiotics during or following anti-cancer therapies.

CONCLUSION

The association with gut resident microbiota and their host is very heterogeneous. Intestinal microbiota progresses and changes with diet, aging and overall exposure to complex environment in functional studies, underlined the significant role of gutmicrobiome in cancer therapy. Genetics, together with functional studies, underlined the key role of gut microbiome in cancer. Certain bacterial subpopulations have the capacity to increase during gut dysbiosis in turn to trigger the development of an inflammatory and pro-cancerogenic environment. On the other side, numerous probiotics derived from gut are capable to safeguard the host, re-storing the circumstances of a healthy intestinal microbiota within dysbiotic patients, especially in cancer patients. A well-established probiotic example in cancer is LGG, frequently administered as corresponding therapeutic to treat dysbiosis. By the identified functions as anti-inflammatory and anti-cancer agent in cellular and animal models, probiotic can be considered to be further categorized as adjuvant in combined anti-cancer treatments in the future.

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