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Review article

The impact of tumor and gut microbiotas on cancer therapy: Beneficial or detrimental?

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ABSTRACT

Cancer is a globally challenging health problem threatening mankind. Despite therapeutic advances in dealing with this malignancy, heterogeneous response and resistance to chemotherapeutic agents remain the hallmarks of cancer therapy. On the other hand, the involvement of the microbiota in affecting human health is well defined. An ever-growing body of evidence implicates the potential link between the microbiome and the efficacy of cancer therapies. Gut microbiota can modulate the metabolism of drugs in a number of ways. The presence of bacteria within the tumor environment can also impact the responses to cancer therapies; changing the chemical structure of chemotherapeutic drugs, affecting their activity, and local concentration. However, the underlying mechanisms by which gut and tumor microbial communities affect the response to cancer therapy are poorly understood and deciphering these mechanisms is of paramount importance. This review provides an overview of how gut and tumor microbiota might affect the efficacy of chemotherapy, radiotherapy, and immunotherapy and alleviate the adverse side effects of these therapies for the development of personalized and effective anticancer therapy.

1. Introduction

Cancer is the foremost cause of mortality worldwide. In spite of therapeutic advances in the realm of cancer, heterogeneous response and resistance to chemotherapeutic agents remain the hallmarks of cancer therapy. Chemo-resistance leads to relapse, metastasis, and reduction in patients' survival. There are different cell-intrinsic mechanisms including drug transporter pumps, autophagy, inhibition of apoptosis, DNA damage repair, and genomic instability as well as cell-extrinsic factors such as tumor microenvironment (TME) that are involved in chemo-resistance [1,2]. Recently, published studies have also highlighted the impact of commensal bacterial species in the metabolism, efficacy, and toxicity of chemotherapeutic drugs [3,4].

The gut microbiome exerts a big impact on both human health and disease. Evidence supports the contribution of gut microbiota in carcinogenesis. In mammalian cells, microbial-produced toxins contribute to carcinogenesis via inducing DNA damage and genomic instability [5]. *Bacteroides fragilis* toxin (Bft) causes DNA damage indirectly by the up-regulation of spermine oxidase (SMO) in colonic epithelial cells, resulting in the production of reactive oxygen species (ROS) and DNA damage [6,7]. Whereas, cytolethal distending toxin (CDT) and colibactin can directly cause double- stranded DNA (dsDNA) damage and consequently trigger DNA repair in host cells [5,7]. In addition to microbial toxins, other microbial proteins are involved in cancer progression through participating in host pathways such as Wnt/β-catenin signaling pathway [8]. Beyond their function in carcinogenesis, gut and tumor microbiotas are reported to be involved in response to cancer therapy [9]. The presence of bacteria can also impact other aspects of cancer development such as cell proliferation, angiogenesis, invasion, tumor immunity, and metastasis that can be significant

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avenues for future research [4].

Gut microbiota is extremely involved in the alteration of the mammalian immune responses [10] and affects the chemotherapy efficacy through modulating the host response. On the other hand, the antitumor chemotherapeutics generally cause the gut dysbiosis, causing the alteration of host immune responses and severe intestinal side effects. In addition to the impact of gut microbiota in cancer therapy, the presence of microbiota within the tumor niche can modulate the response to therapy. Tumor microbiota can change the chemical structure and activity of chemotherapeutic agents [11,12].

Knowing the critical roles of gut and tumor microbiota in drug metabolism, any alteration in microbiota can be associated with the inter-individual differences to cancer therapy. Consequently, understanding the impact of microbiota on metabolism, efficacy, and toxicity of chemo-drugs will progress the designing of rational drug and ease the personalized medicine. In this review, we will focus on cancer therapy and chemo-resistance through the lens of the human gut and tumor microbiota.

2. Gut microbiota

Human microbiome research is a burgeoning and exciting field of research nowadays [13,14]. The human microbiota homes approximately 100 trillion communities of microorganisms (i.e. mostly bacteria, archaea, fungi, and viruses), which colonize in different epithelial surfaces within the body from birth and can be considered as a "separate organ" [15–17]. The composition of the microbiota is shaped by host genetics, age, race, type of birth delivery, feeding regimen, an individual's lifestyle, as well as the environmental exposures to xenobiotics and antibiotics [18,19]. This variation in composition to the microbiome community makes it as diverse as a human fingerprint [20]. Microbiota composition evolves during the first years of life before maturation into an adult like microbiota. After that, the composition of the microbiota in the gut and other epithelial barriers remains relatively constant throughout life, although it could still be affected by diet, changes in lifestyle, diseases, and disease treatment [13–15,18].

The gut microbiota can impact a large number of physiological and pathological processes, including metabolism, synthesis of vitamins, the integrity of the gut mucosal barrier, immunomodulation, and protection against pathogens. For these reasons, the microbiota is frequently termed the "hidden organ" or the "forgotten organ" [13–15,17,18,21–23]. In order to fulfill these tasks, this so-called "forgotten-organ" establishes a balance within the host, a condition referred to as eubiosis [24,25]. Perturbations of this balance, often manifested as microbial dysbiosis, have been associated with different diseases, including inflammatory diseases, metabolic diseases, and cancers [14,17,19,22–24]. It is worth mentioning that microbial dysbiosis has a dual role in cancer, it may contribute to cancer pathogenesis and progression [13,26], it may affect the therapeutic outcome [17] as a result of the microbial ability to metabolize drugs and xenobiotics, and modulate host inflammation and immune responses [15,24].

3. Interplay between gut microbiota and cancer therapy

The interaction between human microbiome and drugs was proposed as pharmacomicrobiomics by ElRakaiby et al. in 2014 that covers the effect of microbial flora on drug fate, efficacy, and toxicity [27]. Despite published reports on the subject, understanding the connection between them remains incomplete [28]. There is a sheer necessity to evaluate the cross-talk between chemotherapeutics and the microbiome to define how these interactions or metabolic byproducts may help medicine develop personalized cancer therapies [29]. The dual impact of gut microbiota on altering the chemotherapeutic agents and vice versa raised a philosophical dilemma, is it cause or effect? In the following sections, we try to highlight the reciprocal interaction between gut microbiota and cancer therapy.

3.1. Impact of cancer therapy on gut microbiota

Gut microbiota affects the response to cancer therapy, whereas cancer treatment impacts the microbiota. Chemotherapy can induce dysbiosis and affect different metabolic pathways. Antibiotics prescribing is increased during the chemotherapy which effects the microbiota, while there is some evidence indicating that simultaneous antibiotic consumption during therapy effects the efficiency of cancer immunotherapy negatively. Moreover, the administration of antibiotics and/or osmotic bowel preparations can also disrupt the microbiota during the surgery [9].

3.2. Gut microbiota and response to chemotherapy

It is evident that the gut microbiota may play a crucial role in regulating responses to cancer therapy. Data from preclinical models have revealed that the microbiota of gut as well as other body sites can modulate the host responses to chemotherapy. Research has shown dual effects of microbiota on chemotherapeutics in this respect. For instance, cyclophosphamide may exert systematically favorable anticancer effect via maturation of Th-17 cells within lamina propria and effector lymph nodes as a result of bacterial translocation in a process known as leaky gut [30,31].

3.3. Microbiota and cytokine-based therapy

The microbiome may affect cytokine-based therapies (e.g., interleukin 2 (IL-2), interferons (IFNs)), since gut microbial dysbiosis results in aberrant immune responses via the abnormal production of inflammatory cytokines (Fig. 1). Related research has revealed an important correlation between microbial commensals and systemic immune responses that is regulated via the production of tumor necrosis factor α (TNF-α) and INF-γ which in turn was involved in specific microbial metabolic pathways like palmitoleic acid metabolism and tryptophan degradation to tryptophol [32–35]. Studies demonstrated that inter-individual variability in immune responses is due to gut microbiome variations as well as cytokine variations that are regulated by the microbiome. Ever-growing evidence has suggested that microbial metabolites lessen pathogen-induced TNF-α production, which shed light on how the gut microbiota may impact cytokine-based therapies [31–33]. The cross-talk between microbiome and cytokine-based therapies that affects the pathophysiology of oncological responses is yet under investigation [32–35].

3.4. Gut microbiota and radiotherapy

There is just too little data on the possible effect of the microbiota on ionizing radiation treatment. Radiotherapy destroys the interplay between the host and microbiota by damaging the proliferating epithelia such as the gut and skin. Furthermore, microbiota is altered by radiation, and according to the studies in this field, the gut microbiota profile could be used as a predictive biomarker for the radiotherapy-associated toxicity [35]. In the model of radiation proctitis, radiation induced localized dysbiosis in mucosal microbiota of irradiated mice by increasing the abundance of *Proteobacteria* and decreasing the *Bacteroidetes* and *Firmicutes* diversity. This alteration in microbiota was connected with postradiation tissue injury. This group of microbiota induced the production of inflammatory cytokines, such as IL-1β and TNF-α [7,36].

3.5. Microbiota and adoptive cell therapies

Gut microbiota plays a critical role in the effectiveness of adoptive cell therapies (ACT). ACT including tumor-infiltrating lymphocytes

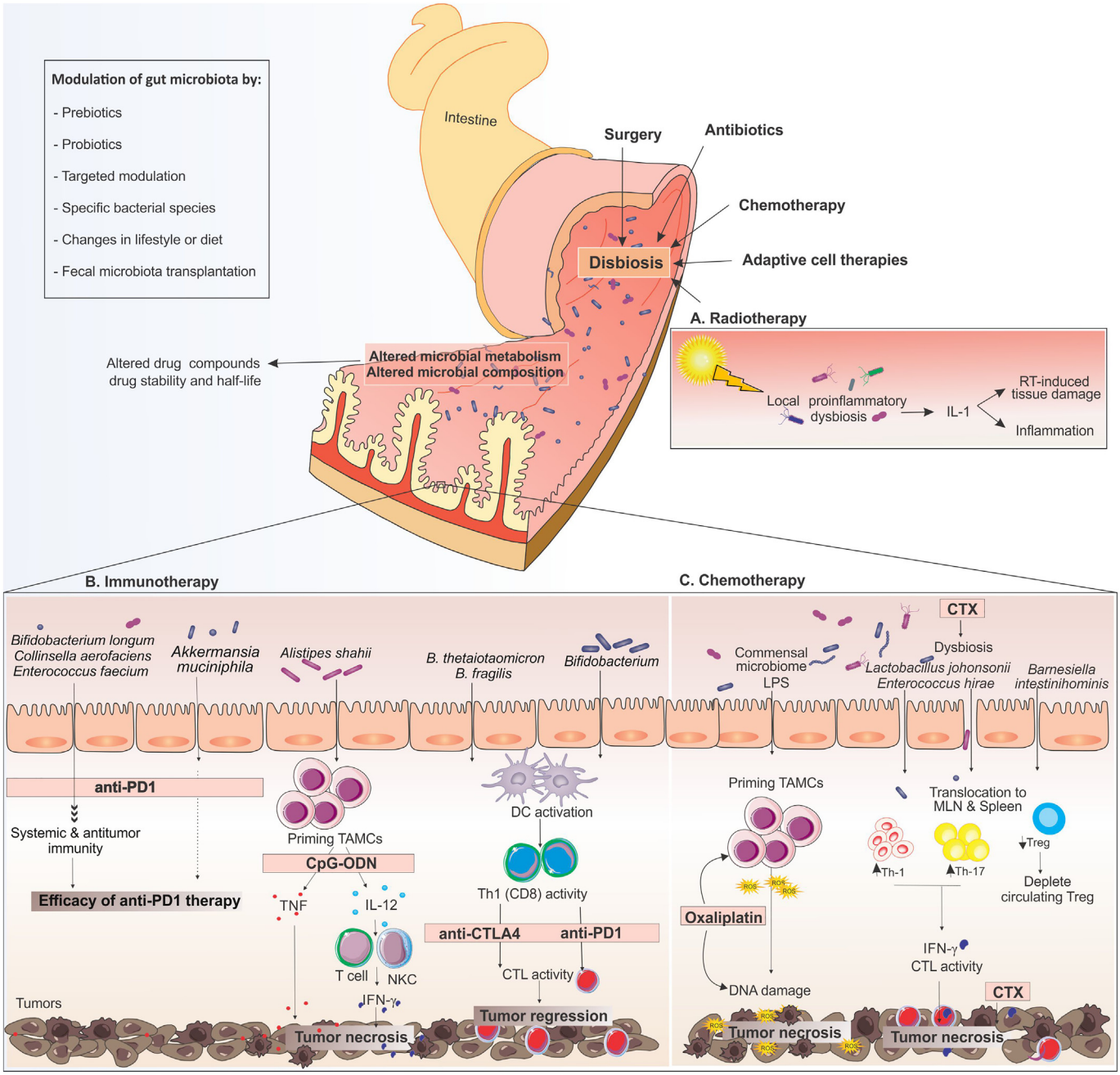

Fig. 1. Gut microbiota and cancer therapy. (A) Radiation therapy can alter the microbiota composition. Further, it induces localized dysbiosis, which may associate with post radiation tissue damage. Dysbiosis play a role in intestinal inflammation and tissue damage by induction of inflammatory cytokines, such as IL-1b and TNF-α [36]. (B) Recent evidence highlighted the interaction between the microbiota and response to immunotherapy. In this regard, CpG-ODN exerts potent immune-stimulatory properties and antitumor activity via induction of pro-inflammatory cytokine production (i.e. TNF and IL-12) and Th1-type immune responses [15,24,43]. Besides, the immune checkpoint inhibitors include CTLA4 and PD1 or its ligand (PDL1) act as strong immune-therapeutics in many types of cancers. Similarly, studies demonstrated that there is an interplay between commensal microbial composition and anti-tumor responses of anti-CTLA-4 and PD-1 by inducing maturation of dendritic cells and a Th-1 response [15,47]. (C) Emerging evidence suggested that the gut microbiota may play a crucial role in regulating responses to chemotherapeutics. In this regard oxaliplatin exerts its anticancer effect via ROS production. The gut microbiota stimulates ROS production via tumor-associated myeloid cells. Excessive ROS results in oxidative stress which led to oxaliplatin genotoxicity and triggers the death of cancer cells [50]. Cyclophosphamide alters the composition of gut microbiota and induces translocation of commensal bacteria to secondary lymphoid organs. In the lamina propria, the bacteria, mediated the maturation of pro-inflammatory T cells (Th-1 and Th-17 cells) and destroy immunosuppressive T cells in order to induce the anticancer efficacy [23,50].
CTX, cyclophosphamide; LPS, lipopolysaccharide; MLN, mesenteric lymph node; Th, T helper; Treg, regulatory T cell, IFN, interferon; ROS, reactive oxygen species; TAMCs, Tumor-associated myeloid cells; CTL, Cytotoxic T lymphocytes; IL, interleukin; RT, radiation treatment; TNF, tumor necrosis factor; DC, dendritic cell; NKC, natural killer cell; CD, cluster of differentiation; anti-PD1, anti-programmed cell death protein 1; CTLA-4, cytotoxic T lymphocyte associated antigen 4; CpG-ODN, CpG oligodeoxynucleotide.

therapy, endogenous cell therapy, chimeric antigen receptor (CAR) T cell therapy, and genetically engineered T-cell therapy result in objective responses in cancers. $CD8^+$ and $CD4^+$ T cells are widely used to achieve antigen-driven responses in ACT, whereas the combination of lymphodepletion preconditioning procedures with ACT results in better outcomes. Lympho-depletion increases the therapeutic efficiency of adoptively transferred cells via toll-like receptor 4 (TLR) by removing cytokine sinks from natural killer (NK) cells and immunosuppressive cells and probably by modulating the translocation of microbial products [37,38].

4. Microbiota and anticancer therapy: tThe mechanistic framework

In 2017, Alexander et al. suggested a "TIMER" framework, depicting the mechanisms by which gut microbiota can modulate the outcomes of anticancer therapy. The proposed term stands for translocation, immunomodulation, metabolism, enzymatic degradation, and reduced diversity [39,40]. Translocation of bacteria is defined as the passing of pathogenic or commensal bacteria across the leaky gut into the systemic circulation, leading to the morbidity of chemotherapy. The immunomodulation of host immune responses by gut microbiota has an essential function in the stimulation of immune response caused by chemotherapeutic agents. Metabolism of chemotherapeutic agents can be also mediated by different microbial enzymes. Moreover, metabolites can exert toxic effects after their entrance into the intestine via the liver or bile ducts. The bacterial enzymatic degradation can also impact drug response. Bacterial beta-glucuronidases enzyme can cause diarrhea in cases who are under CPT-11 (also called irinotecan) colon cancer therapy. Reduced bacterial diversity and change in microbiota composition are other possible mechanisms by which microbiota influence drug responses [41]. In the following sections, we will have a close look at different aspects of the "TIMER" framework, further, we will focus on microbiota-induced chemo-resistance.

4.1. Microbial immunomodulation

So far, it has been suggested that the microbiota plays an important role in altering the response to immunotherapy, thus targeting the cross-talk between microbiota and immune cells are under active investigation by researchers [15,24,42,43].

4.1.1. CpG-oligodeoxynucleotide (CpG-ODN)

CpG oligodeoxynucleotides are synthetic TLR-9 ligands containing un-methylated CG dinucleotides and mimicking bacterial DNA which have shown potent immune-stimulatory properties (induce pro-inflammatory cytokine production (i.e. TNF and IL-12) by myeloid cells [15] and TH1-type immune responses) and antitumor activity in several kinds of cancer [24,43]. The impediment of tumor growth is through the production of TNF by tumor-associated myeloid cells [43]. Preclinical studies in mice bearing EL4 lymphoma, MC38 colon carcinoma, and B16 melanoma have also shown that subcutaneously administered CpG-ODNs stimulate a tumor-eradicating immunological response [44]. The survival rate and the induction of TNF were reduced significantly in germ-free and/or ABX-treated mice, which in turn highlight the microbiota's vital role in enhancing CpG-ODN efficacy [44]. Animal experiments confirmed that the *Alistipes shahii*, a Gram negative bacterium, increases while *L. fermentum* reduces the CpG-ODN response [44]. Furthermore, research showed that the oral administration of a known bacterial species - *Alistipes shahii* - could renovate TNF production by tumor-associated myeloid cells in ABX-treated mice [15,24,45]. Moreover, the oral administration of lipopolysaccharide (LPS) - TLR4 agonist- to germ-free mice restores the responsiveness of the myeloid cells [15]. Hence, the alternation in gut microbiota composition could affect the response to immunotherapies [15].

4.1.2. Immune checkpoint inhibitors

Antibodies that block immune inhibitory pathways signify a novel and thrilling anticancer strategy. These antibodies target suppressive receptors that regulate T cell activation negatively. The immune checkpoint inhibitors include antibodies targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4), also known as CD152; a T cell surface receptor) [24,46] and programmed cell death protein 1 (PD1) or its ligand (PDL1) that act as strong immunotherapeutics in many cancers [15,46,47]. Nevertheless, germ-free or antibiotic-treated mice did not respond to CTLA and/or PD-1 blockade [48,49]. Studies suggested that there is an interplay between commensal microbial composition and anti-tumor responses of anti-CTLA-4 and PD-1, however, researchers have only observed a modest overlap in microbial composition across different study cohorts [45,50]. In this regard, evidence demonstrated better anti-tumor responses in mice harboring *Bifidobacterium* [23,43,47]. Studies showed a strong association between *Bifidobacterium* and T cell response, further, oral administration of a cocktail of *Bifidobacterium* species combined with an anti-PD-L1 antibody nearly could abolish cancer cell growth [49]. *Bacteroides* (*Bacteroides thetaiotaomicron*, *Bacteroides fragilis*) are among other bacterial species that were responsible for CTLA-4 blockade through the induction of a Th1 immune response [24]. In this respect, research confirmed that the oral administration of either *B. thetaiotaomicron* or *B. fragilis* restores the therapeutic response to anti-CTLA-4 by inducing maturation of dendritic cells and a Th-1 response in germ-free mice [48]. Moreover, it has been revealed that fecal levels of *Akkermansia muciniphila* – a species belonging to the *Verrucomicrobiaceae* family - is positively correlated with a satisfactory response to immunotherapy [23,51]. Likewise, the oral administration of *A. muciniphila* could enhance anti-tumor efficacy [23,24]. The aforementioned studies highlighted the promising interaction between gut microbiota and the efficacy of therapeutic strategies applied to cancer.

4.2. Gut microbiome and chemo-drug metabolism and toxicity

The ultimate goal of designing anticancer drugs is exploring the effective treatments of malignancies, but major inconvenience in anticancer treatments is the development of drug resistance, recognized as the primary cause of chemotherapy failure in most human tumors. Recently, increasing studies have shown that gut microbiota promotes chemo-resistance beyond improving the treatment efficacy [52] and therapy. Some chemotherapeutic drugs affected by gut microbiota will discuss below.

4.2.1. Irinotecan

Irinotecan hydrochloride (CPT-11) - a topoisomerase-1 inhibitor- is a key chemotherapeutic agent that is used in combination with other anticancer drugs in the treatment of several types of cancers mainly metastatic colorectal cancers (CRC) [21,53]. However; CPT-11-induced toxicity (severe diarrhea) upon its activation and subsequent metabolism [45,53,54], prevents dose-intensification, and in severe cases, results in early termination of treatment though limiting its clinical application [41,43]. After intravenous administration, CPT-11 is converted to its active form, SN-38, upon the removal of a piperidino moiety by carboxylesterases [19,24,41,45,54]. Toxicity of this active metabolite is due to damaged crypt cells of the cecum, as well as inducing submucosal inflammation [43]. Subsequently, SN-38 is detoxified by host hepatic uridine diphosphate (UDP)–glucuronosyltransferase enzymes by coupling it to a glucuronidate moiety producing SN-38G, and being excreted into the gastrointestinal tract via the biliary ducts [19,24,41,45,54]. It is reported that irinotecan toxicity to different parts of the intestine is not associated with carboxylase activity of intestinal tissue, but with the lumen β-glucuronidase activity and it is evident that the gut microbiota has the potential to alter the chemotherapeutic drug. Resident microbial β-glucuronidases in the intestines can convert the inactive SN-38G to the active and toxic SN-38

by the removal of the glucuronide group as a carbon source [21,24,54]. CPT-11 itself intensifies toxicity via augmented colonization of the gut by β-glucuronidase-producing species such as *Escherichia coli* (*E. coli*), *Staphylococcus* spp., *Clostridium* cluster XI, and *Enterobacteriaceae* [55–57].

For preventing dose-limiting diarrhea resulting from CPT-11 therapy, alternative strategies were applied. It has been shown that the administration of antibiotics reduced the number of β-glucuronidases producing bacteria, though suppressing CPT-11 cytotoxicity [43]. In this regard, studies in rat models showed that amoxapine were effective in suppressing diarrhea associated with CPT-11 [41,45]. Another alternative is the development of bacterial-specific inhibitors, which selectively inhibit β-glucuronidase since they possess unique motifs (bacterial loop) [41,43,45]. This useful modality may have utility as novel therapeutics and can improve patient outcomes and their life quality [43].

4.2.2. Oxaliplatin

Oxaliplatin is a platinum-based anticancer drug used to treat several gastrointestinal malignancies. Its mechanism of action relies not only on the formation of platinum-DNA adducts/cross-links which blocks DNA replication and production of ROS, but also on their ability to stimulate immune response [23,24,50]. Oxaliplatin's efficacy depends on both microbiota and the immune system. ROS production in tumor-infiltrating myeloid cells is stimulated by the gut microbiota [19,53]. High levels of ROS result in oxidative stress which leads to oxaliplatin genotoxicity and triggers the death of cancer cells [50]. Mechanism-based studies suggested that TLR4-MYD88 signaling pathway is involved in this procedure [38,47]. The disruption in intact gut microbiota composition drops the efficacy of oxaliplatin, suggesting the key role of microbiota in altering the efficacy and toxicity of several chemotherapeutic agents [43]. In this respect, research in germ-free/antibiotic-treated mice models showed a reduction in microbiota- induced ROS production that results in chemotherapy failure [23,24,47,50], but therapy rescued by LPS administration [43]. Moreover, oxaliplatin can induce the translocation of specific bacterial species (i.e. *Lactobacillus johnsonii* and *Enterococcus hirae*) from the intestinal lumen into secondary lymphoid organs, resulting in initiating Th1 memory responses against commensals that cross the intestinal barrier [38]. Interestingly, researchers stated that other chemotherapeutic agents, such as alkylating agents, anthracycline, pavonlotoxin, camptothecin, and podophyllotoxins perform the same way as platinum-based chemotherapeutics through high levels of ROS production [50]. These data highlight the impact of gut microbiota manipulation on improving cancer therapy [44,58].

4.2.3. Cyclophosphamide

Another clinically important chemotherapeutic agent is cyclophosphamide (CTX) - an alkylating agent used in hematologic malignancies and solid tumors - [19,23,43]. It exerts its antitumor activity by stimulating the antitumor immune response, yet it controls tumor growth by inducing Th-1 and Th-17 cells and destroying immunosuppressive T cells [50]. CTX treatment alters the gut microbiota composition via the disruption of gut epithelial barrier, which results in commensal bacteria (*Lactobacillus johnsonii*, *Lactobacillus murinus*, *Enterococcus hirae*, and segmented filamentous bacteria (SFB), as well as the Gram-negative bacterium *Barnesiella intestinihominis*) translocation into the secondary lymphoid organs (mesenteric lymph nodes and spleen) [23]. There, the bacteria mediated the differentiation of pro-inflammatory T cells (Th-1 and Th-17 cells) to induce anticancer efficacy [23,24,43,47,50]. Recent evidence showed that in germ-free/antibiotic-treated mice, the immune reaction of Th-17 was reduced and chemo-resistance to CTX occurred [23,43,50]. Another study determined that providing germ-free mice with some Gram-positive bacterial strains (*L. johnsonii* and *E. hirae*) improved the efficacy of CTX via stimulating Th-17 and Th-1 cells [19,43], this in turn, suggests the significance of gut microbiota in CTX efficacy [53,58].

4.2.4. Microbiome and drug toxicity

Toxicity occurs when the bacterial transformation of a drug leads to the generation of metabolites that have harmful effects on the host. Bacterial enzyme β-glucuronidases participate in the CPT-11 toxicity. The toxic SN-38 leads to diarrhea by effecting the absorptive and secretory characteristics of the intestinal epithelium [59]. Likewise, following Ipilimumab therapy, *Bacteroidetes* induce the production of vitamin B that promotes colitis risk [60].

4.3. Microbiota and chemo-resistance

Understanding the impact of anticancer drugs on the variation of gut microbiota may clarify the processes of chemo-resistance; consequently, assisting to set up approaches to increase the efficiency of treatment [17]. A flurry of evidence demonstrates that inflammation and microenvironment of the tumor may have an essential role in facilitating chemo-resistance. Emerging evidence revealed that there is an intriguing link between the gut microbiota and chemo-resistance [14,61]. In recent times, the bacterium *Fusobacterium nucleatum* has aroused considerable attention as a causative agent in CRC recurrence [62]. *F. nucleatum* is a non-sporulating anaerobic and Gram-negative bacterium that is indigenous of the primate's oral cavity commensal [16,42]. Preliminary studies suggested that *Fusobacterium*, *Coriobacteriaceae*, *Roseburia*, and *Faecalibacterium* are present in colon cancer cells [16,61,62]. Among the aforementioned strains, *Fusobacterium* exists in high abundance in CRC which may indeed promote tumorigenesis besides being associated with poor prognosis [16,42,62]. Further reports showed that *F. nucleatum* may protect tumor cells against chemotherapy thus leading to chemo-resistance in CRC patients [47,50]. For example, co-culturing *F. nucleatum* with HCT-116 colon cancer cells result in reduced apoptosis induced by 5-fluorouracil (5-FU) and oxaliplatin [42].

The molecular mechanism of chemo-resistance triggered by *F. nucleatum* has been elucidated. To date, it is clear that the underlying molecular pathway is via the modulating autophagy pathway. It has been suggested that the formation of autophagosomes, the induction of autophagy-related proteins (i.e. pULK1, ULK1, and ATG7) [61], and the downregulation of miRNA-18a and miRNA-4802 via a TLR4/MYD88-dependent-mechanism [42,47,50] are the main pathways involved in *F. nucleatum* induced chemo-resistance [61,63]. Studies showed that the downregulation of these two miRNAs activates autophagy and results in the development of chemo-resistance [14,16].

A recent study demonstrated that *F. nucleatum* infection could decrease the CRC cells chemosensitivity to 5-FU both in vitro and in vivo via upregulation of BIRC3 expression, an inhibitor apoptotic protein that prevents apoptosis via direct inhibition of the caspase cascade. BIRC3 expression can be regulated by TLR4/NF-κB pathway in CRC cells co-cultured with *F. nucleatum*. Moreover, a high abundance of *F. nucleatum* is associated with chemoresistance in patients with advanced CRC [64]. Moreover, studies in mice models recommended that applying antibiotics to eliminate *F. nucleatum* effectively improves the efficacy of chemotherapeutics [14]. Furthermore, recent studies suggested that *F. nucleatum*'s adhesion FadA interacts with the host's E-cadherins, which in turn activates Wnt/β-catenin signaling and can promote inflammation and tumorigenesis [16,62]. A rise in the number of *F. nucleatum* in CRC patients may be a predictive tool of the disease aggressiveness, occurrence of chemo-resistance, and poor outcomes in patients [61,62].

F. nucleatum also promotes a pro-inflammatory microenvironment in the colon and suppresses host immunity; consequently, mucosa immunity inhibition favors tumor growth. Through RadD, Fap2, and FadA, this pathogen binds to the epithelium of colon and attacks the mucosa. This invasion leads to the infiltration of immune cells and the production of cytokines that promote cell proliferation. Additionally, in

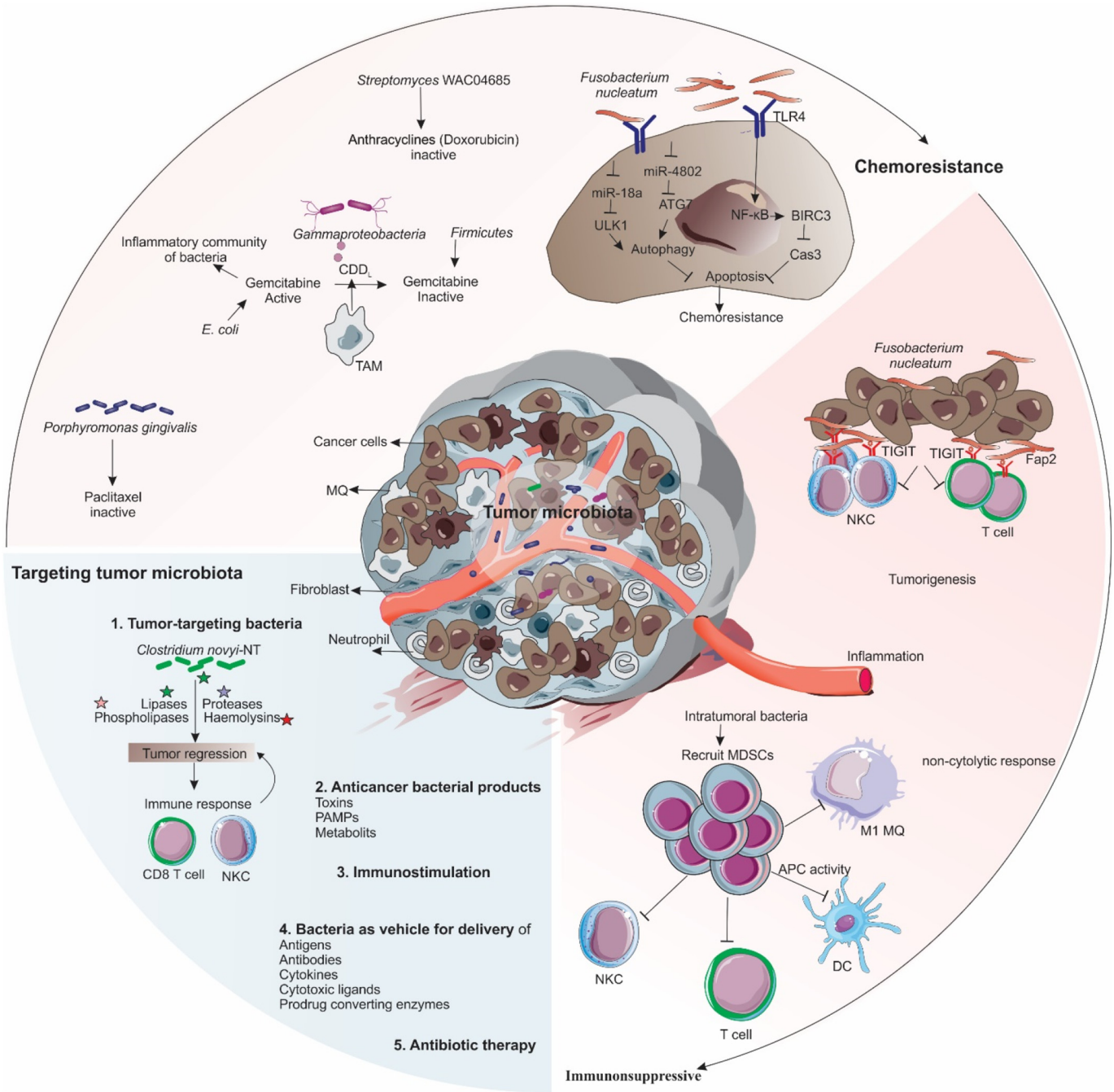

Fig. 2. Tumor microbiota and cancer therapy. Bacteria within the tumor environment can influence the responses to cancer therapies via alternation the structure of chemotherapeutics. In this regard, the evidence demonstrated that *Gammaproteobacteria* inactivate gemcitabine by CDD production which results in chemo-resistance [11,12,24]. Furthermore, intratumoral bacteria can exert both immunosuppressive and immunostimulatory activity. In response to bacteria, innate immune cells within the tumor, stimulate the production of pro-inflammatory cytokines which in turn increase antitumor immune responses. On the other hand, intratumoral bacteria can exert immunosuppressive role via recruitment of MDSCs and production of immunosuppressive cytokines [76–78]. Nowadays targeting tumor microbiota is of great importance. Due to the hypoxic microenvironment and necrotic regions of tumors, anaerobic bacteria reside there. In this regard, studies showed that *Clostridia* spores can germinate in anoxic areas of tumors which can produce extracellular enzymes consequently damage cancer cells and initiate an immune response mediated by NK and $CD8^+$ T cells. Exploiting genetically engineered bacteria in order to accumulate in tumor necrotic areas may help bacteria produce an antitumor immune response or directly kill the tumor cells. They can function as bacterial vehicles to carry bacterial toxins, chemotherapeutics, cytokines, and immune activating proteins into tumors [84–86]. CDD, cytidine deaminase; TAM, tumor-associated macrophages; TLR, toll-like receptor; NF-KB, nuclear factor kappa-light-chain-enhancer of activated B cells; NKC, natural killer cell; MQ, macrophage; APC, antigen presenting cell; DC, dendritic cell; MDSCs, myeloid-derived suppressor cells; PAMP, pathogen associated molecular pattern; TIGIT, T cell immunoglobulin and ITIM domain.

the colon mucosa, this bacterium interacts with the immune cells and increases dendritic cells, M2 macrophage polarization, and tumor-associated neutrophils that reduce anti-tumor immunity. *F. nucleatum* also prevents the activity and cytotoxicity of respectively T and NK, restricting their ability to fight against colon adenocarcinoma [65,66].

Geller et al. found the existence of different bacterial species inside of pancreatic tumor tissues and microenvironment and examined their roles in gemcitabine (2′,2′-difluoro-2′-deoxycytidine; dFdC) chemo-resistance [12]. Intratumor microbes can produce the cytidine deaminase (CDD) enzyme. Gemcitabine can be metabolized into its inactive

metabolite by long form of CDD (CDD_L). Gammaproteobacteria, the common bacterial species in pancreatic cancer tissues, can express CDD_L and cause a reduction in response to gemcitabine; however, this resistance to gemcitabine could be neutralized by ciprofloxacin antibiotic [67]. It is also specified that other microenvironmental component can also affect CDD activity. Tumor-associated macrophages (TAM) can lead to chemo-resistance through inducing CDD upregulation [68]. The *Firmicutes* phylum may also inactivate gemcitabine [67]. It is also reported that the effectiveness of gemcitabine can be influenced by *E. coli* in human tumors [11]. Overall, Gemcitabine therapy may choose an inflammatory community of bacteria that might impact the clinical outcome [67].

Streptomyces WAC04685 could inactivate anthracyclines (e.g. doxorubicin) through a deglycosylation mechanism that is mediated by the NADH dehydrogenase [69]. Moreover, the efficacy of numerous fluoropyrimidine nucleoside-based anticancer drugs can be affected by the presence of mycoplasma species. Therefore, these chemotherapeutic agents must be combined with a specific antibiotic or inhibitors against mycoplasmas to avoid plasma or/and tumor site inactivation of the drug [70,71].

It is suggested that one of the most significant factor in modifying chemo-resistance and creating metastatic lesions is inflammatory responses. *Porphyromonas gingivalis* is a major pathogenic bacterium that is involved in the chronic inflammatory situation of the oral cavity (periodontitis). In oral squamous cell carcinoma, *P. gingivalis* can mediate resistance to paclitaxel via a Notch1 dependent mechanism [72].

4.4. Microbiome and reduced diversity

Further studies need to be developed in order to understand the interactions between chemotherapy and microbiota. Chemotherapy plays an important role in the alteration of gut microbiota structure after treatment, for instance, the microbial abundance and diversity of anaerobes and *streptococci* decreased, whereas *Bacteroides* increased in mucositis-developed rats treated with methotrexate [73]. In another study, the abundance of *Proteobacteria* was enhanced, but *Firmicutes* and *Actinobacteria* decreased in patients with non-Hodgkin lymphoma treated with myeloablative chemotherapy [73]. There is a reduction in the abundance of the taxa such as *Firmicutes* and *Actinobacteria* after chemotherapy, which are responsible for decreasing inflammation through NF-κB pathway modulation. *Firmicutes* abundance is negatively correlated with metabolic pathways associated with intestinal inflammation, including cell motility, glycan metabolism, and xenobiotic degradation [41,74].

5. Tumor microbiota

Beyond gut microbiota, the presence of bacteria within the tumor environment can also impact the responses to cancer therapies, bacteria can change the chemical structure of chemotherapeutic drugs, affecting their activity and local concentration [11,24].

In pancreatic tumors, Gammaproteobacteria produce a CDD [75] isoform that inactivates gemcitabine, resulting in lower local drug concentrations and chemo-resistance [11,12].

Furthermore, in CRC, intratumoral *Fusobacterium* may confer resistance to chemotherapy via the aforementioned mechanisms (explained earlier) [63]. Furthermore, intratumoral bacteria can exert immunomodulatory functions; creating immunosuppressive or immunostimulatory microenvironments. In animal models, innate immune cells within the tumor can recognize bacteria, stimulate the production of proinflammatory cytokines that drive a further influx of immune cells into the tumor microenvironment and increase antigen presentation, thereby expand antitumor immune responses [76,77].

Intratumoral bacteria can be immunosuppressive, they can recruit myeloid-derived suppressor cells (MDSCs) and elevate the immunosuppressive cytokines production or the alternative immune checkpoints activation, and leading to a non-cytolytic response [78]. For instance, *Fusobacterium*-bound tumors use immune evasion mechanism. *Fusobacterium*'s Fap2 protein can bind to the immune cells inhibitory receptor TIGIT (T cell immunoglobulin and ITIM domain) on NKC and T cells and inactivate their cancer-killing ability [65], Fig. 2. Antibiotic therapy could decrease the intratumoral bacterial load in pancreatic cancer that could elevate the innate effector cells recruitment and cytolytic T cell activity by decreasing the recruitment of suppressive cells into the tumor microenvironment [78].

6. Gut microbiota as a cancer therapy target

The modulation of gut microbiota can improve cancer therapeutic responses and/or abolish treatment-induced toxicity. The gut microbiota modification can be mediated through fecal microbiota transplantation, changes in lifestyle or diet, administration of prebiotics, probiotics or specific bacterial species. Moreover, the targeted modulation of gut microbiota can be achieved by bacteriophages or tailored antibiotic treatments (reviewed comprehensively in Ref. [9]).

Diet is one of the effective factors in controlling the composition of the gut microbiota. Emerging data support the interaction between diet-microbiota-chemotherapy. Beyond diet, food supplements, probiotics, prebiotics, synbiotics, and postbiotics may also be used to modulate gut microbiota [9,41]. Animal studies demonstrated that mice fed a diet high in protein, L-lucine, fish oil, and specific oligosaccharides showed significant reduction in *Pseudomonas aeruginosa* population, during CTX induced immune suppression in comparison to isoenergetic control diet [41]. Moreover, fasting may reduce the adverse effects of chemotherapy. Data demonstrated that fasting improved the vomiting associated to doxorubicin treatment, further, fasting may protect dogs - as model animals - from side effects of irinotecan treatment [41]. Besides, data from research showed the beneficiary effects of gut microbiome metabolism and some food supplements such as ginseng, ellagic acid, and polysaccharides from the ink of the squid *Ommastrephes bartramii*, which may potentiate some chemotherapeutics efficacy and protects against adverse side effects [41]. So far, performed studies with different strains of probiotics showed reduced episodes of diarrhea as a result of chemotherapies. Further, consuming prebiotics (i.e. oligofructose and inulin) enhanced the effect of chemotherapeutics in mice models via selective stimulation of growth of specific bacterial taxa and alternation of short-chain fatty acids (SCFA) levels within the gut [41,79]. Postbiotics have also been studied, like butyrate, which potentiates the anticancer effects of chemotherapy [9,57,80]. However, careful clinical research should be performed in order to determine the safety of applying them to patients undergoing chemotherapy [9].

7. Tumor microbiota as a therapeutic target

Beyond the alteration of gut microbiota to hinder cancer progression and improve therapies, there are efforts to target tumor microbiota. It is reported that intratumoral bacteria exert a harmful effect on the therapeutic response, in a way that antibiotic administration could enhance the responses to chemotherapy [12,63,78]. It should be taken into consideration that the systemic administration of antibiotic can also impact gut microbiota.

Understanding the tumor microbiome composition and function aides research to target the tumor resident microbes as means of tumor-specific delivery of therapeutic targets or treatment. Specific targeting of tumor microbiota can take advantage of the hypoxic microenvironments and necrotic regions of tumors. Anaerobic bacteria can home the tumors. For instance, *Clostridia* spores germinating in anoxic areas of tumor could produce extracellular enzymes that destroy cancer cell membrane and induce solid tumor regression, initiating an immune response mediated by NKCs and $CD8^+$ T cells, thereby can be an antitumor therapeutic approach [81]. Likewise, attenuated strain of

Clostridium novyi could eliminate neoplastic tissues in animal models and in a human case with advanced leiomyosarcoma [75]. The mechanism by which bacteria drive tumor reduction is mediated by the initiation of anti-cancer immune responses. TNF-α secretion induced by bacteremia, as a vasoactive facilitate the entry of bacteria into the tumor microenvironment [82], resulted in the activation of $CD8^+$ T cell that boost tumor surveillance and clearance [83].

Utilizing genetically engineered bacteria to accumulate in tumor necrotic areas can help bacteria produce an antitumor immune responses or kill the tumor cells directly. In this regard, bacteria may play a range of functions including immune stimulation and cytokine production. They can also function as bacterial vehicles to carry bacterial toxins, chemo drugs, cytokines, and immune activating proteins into tumors (Fig. 2) [84–86]. Moreover, bacteria can express agents within tumors [87]. Bacterial bioengineering strategies can be used to fight against cancer comprehensively [88].

8. Conclusion

Microbiome studies have emerged as a promising area of investigation for cancer therapy over the past decades. Evidence showed that the gut microbiota plays a reciprocal role between the efficacy and toxicity of chemotherapeutic agents. However, the manipulation of the gut microbiota in order to enhance the efficacy of chemotherapeutics and lessen the adverse side effects seems challenging, it is surely worth the effort. Importantly, in cancer therapy, understanding how the human microbiome interacts with chemotherapeutics, leads the microbiota to become an important tool in personalized oncology.

Declaration of Competing Interest

The authors declare no conflict of interest.

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