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From promotion to management: The wide impact of bacteria on cancer and its treatment

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Abstract

In humans, the intestine is the major reservoir of microbes. Although the intestinal microbial community exists in a state of homeostasis called eubiosis, environmental and genetics factors can lead to microbial perturbation or dysbiosis, a state associated with various pathologies including inflammatory bowel diseases (IBD) and colorectal cancer (CRC). Dysbiotic microbiota is thought to contribute to the initiation and progression of CRC. At the opposite end of the spectrum, two recently published studies in *Science* reveal that the microbiota is essential for chemotherapeutic drug efficacy, suggesting a beneficial microbial function in cancer management. The dichotomy between the beneficial and detrimental roles of the microbiota during cancer initiation, progression and treatment emphasize the interwoven relationship between bacteria and cancer. Moreover, these findings suggest that the microbiota could be considered as a therapeutic target, not only at the level of cancer prevention, but also during management, i.e. by enhancing the efficacy of chemotherapeutics.

Keywords

cancer; chemotherapy; dysbiosis; intestinal microbiota; therapeutic efficacy

Introduction

The sheer number of microorganisms – estimated in the trillions – inhabiting the human body surface and its cavities, has been a source of fascination, generating numerous questions about their implication in health and diseases. Remarkably, until recently the scientific community has mostly interrogated the small segment of microbes implicated in infectious diseases. These disease-causing microorganisms have undeniably shaped our view on how devastating microbes could be, not only to human health, but also to numerous forms of life (lifestock, plants, aquatic animals). For example, *Yersinia pestis* alone is thought to have decimated 25% of the world population in the 14th century, and the infectious agent responsible for the disease was only identified 400 years later by Alexander Yersin. The advent of microscopy in the 17th century and the early observation of

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microorganisms by Antoine Van Leeuwenhoek likely galvanized the field of microbiology [1]. The subsequent improvement in microscopy techniques (which allowed the description of various organisms in the 19th century) in conjunction with increasing evidence that some bacteria were causing numerous pathologies, and even death, likely contributed to our collective “fear” of microorganisms. Since the end of the19th century, researchers observed that bacterial infections and the administration of microbial peptides have anti-tumor effects in patients, suggesting bacteria-mediated host immune activation could be harnessed for therapeutic purpose [2]. Indeed, the vast majority of microorganisms inhabiting humans and their immediate environment are not pathogenic entities, but rather symbiotic organisms implicated in essential functions of host homeostasis (nutrition, immunity, development). Until recently, little was known about the identity of these microbes, their individual or collective contribution to homeostasis, and their responsiveness to environmental cues. Recent efforts by various microbiome research consortiums (HMP, MetaHit, CMI, etc.) are generating new insight into bacterial-host interaction at various body sites, as well as establishing the functional consequences of these interactions on health and diseases. Among the various locations harboring microbes, the gastrointestinal tract of various higher mammals has been the subject of intense investigation, likely due to the high microbial content and diversity of this organ.

The microbiota and intestinal health

The gastrointestinal tract is the most densely populated organ of the human body, with a microbial load ranging from 10^1 cells per gram of content in the stomach to 10^{12} cells per gram in the colon [3]. These microbial communities are acquired at birth and progressively mature into a stable and adult-like ecosystem by the age of 2-3 [3, 4]. Advanced high-throughput sequencing and computational biology has permitted the partial characterization of the microbial communities living in the intestine. At the phylum level, the gut microbiota mainly comprises Firmicutes and Bacteriodetes, forming close to 90% of the total ecosystem, followed by lesser contributions from members of Proteobacteria, Verrumicrobioa, Actinobacteria, Fusobacteria and Cyanobacteria[5]. This imposing microbial mass (∼6 pounds of body weight) contains an estimated $\sim 3\times10^6$ genes, providing important metabolic capacity required for both the host and microbial fitness [3].

Microbes modulate various aspects of intestinal physiology and function [5]. For example, during post-natal development, microbes participate in intestinal morphological changes such as architecture of the villus, crypt depth, intestinal epithelial cell proliferation, as well as local angiogenesis. This microbial-dependence on intestinal morphology/function is clearly highlighted in germ-free mice, whose intestine shows defects in villus structure and epithelial cell regeneration compared to conventionally-raised mice. It may seem paradoxical that microbes contribute to the edification of a tight and efficient intestinal epithelial barrier aimed at confining them to the luminal space, but containment of the vast microbial ecosystem is essential for maintenance of intestinal homeostasis. Although microbes and microbial-derived antigens can gain access to the mucosal immune system, these exposures occur through the action of specialized cells and structures such as M cells, Peyer's patches and dendrite projection through the epithelial layer by dendritic cells, all of which assure a controlled up-take of luminal antigens for immune processing [6]. The

concerted action of a tight epithelial barrier and regulated sampling of mucosal antigens are essential to avoid unwanted immune response and perturbation of the microbial ecosystem that could lead to the development of host pathologies.

This symbiotic relationship goes beyond intestinal barrier function, influencing immunity, and pathogen resistance which has been reviewed elsewhere [7]. Microorganisms play a role in the differentiation of innate and adaptive immune cells, maturation of gut-associated lymphoid tissue and promotion of immune tolerance [3]. For instance, *Bacteroides fragilis*, through the action of its cell wall component, polysaccharide A, fosters the differentiation of $Foxp3^+$ T regulatory cells (Tregs), a subset of lymphocytes exhibiting anti-inflammatory properties [8]. Besides microbial structures, microorganisms regulate the state of immune response through their metabolic activities, which are largely directed by the host diet. Ten percent of the host's energy requirement is fulfilled by the microbiota through the production of short-chain fatty acids (SCFAs), namely acetate, proprionate and butyrate, which result from dietary carbohydrate fermentation. Conventionally-raised mice lacking SCFA receptors such as GPR43 or GPR109a or wildtype germ-free mice showed defective Treg populations, suggesting that microbial-derived metabolites (e.g. SCFA) utilized host receptors to immunologically educate mucosal immune cells [9, 10]. The SCFA butyrate enhances Treg development as shown in mice fed butyrylated high-amylose diets, which had greater Fox3p+ differentiation (Treg) and resistance to T-cell transfer induced colitis [11, 12]. Once again, this interdependence between diet, microbes and their metabolic products clearly illustrates the complex symbiosis that has formed over millions years of evolution.

Microbes as contributors to intestinal pathologies

A large body of work shows the pivotal role of bacteria in maintaining intestinal homeostasis, hence it comes as no surprise that microbial community disruption, or *dysbiosis*, has deleterious consequences for the host. Indeed, next generation sequencing of microbial 16S rDNA genes and shot-gun metagenomic analysis showed that patients with IBD have a significantly different biota from healthy individuals. Patients with Crohn's Disease showed a decrease in the carbohydrate metabolizers, Ruminococcaceae, and an increase in Proteobacteria/Enterobacteriaceae compared with healthy controls. Analysis of microbial metabolic pathways active in these patients revealed that carbohydrate transport was increased, likely because of the shortage of SCFA normally produced by Ruminococcaceae [13]. IBD is characterized by dysregulated T lymphocyte effector cells, which display Th1 and Th17 immune activation to the endogenous microbiota, and a lack of immune suppression typically afforded by Tregs [10]. It is likely that decreased abundance of bacterial species implicated in the generation of SCFA has profound consequences for Treg development/activation as mentioned above. However, the functional consequence of microbial dysbiosis on T cell activation/suppression in vivo and in IBD development has not been demonstrated. Experiments using “humanized” mice – that is mice transplanted with human IBD dysbiotic intestinal biome – would help address this question.

Patients with colorectal cancer (CRC) also display a dysbiotic intestinal microbiota, and similarly to IBD, the functional relevance of this phenotype on cancer development is still unknown. Although several studies have shown that various microorganisms such as

Helicobacter spp, enterotoxigenic *Bacteroides fragilis* and *enterococcus feacalis* were able to promote CRC in experimental models, their association to human CRC is still debated [14]. To date, numerous microbiome studies have identified a panel of microorganisms associated with various phases of human CRC development [15]. Among the various microbial candidates, Fusobacterium sp – especially *Fusobacterium nucleatum* – stood out as the most reproducible and robust bacterium associated with human CRC [16-18]. Subsequent functional studies using *F. nucleatum* demonstrated the carcinogenic potential of this microorganism in $Apc^{Min/+}$ mice and in a xenograft model [18, 19]. Another bacterial group, Enterobacteriaceae – especially adherent invasive *Escherichia coli* – are predominant in patients with colorectal cancer [20, 21]. Using the colitis-susceptible $Il10^{-/-}$ mouse model, investigators showed that inflammation fosters the bloom of Enterobacteriaceae *E. coli* as demonstrated by next-generation sequencing, which is associated with development of CRC [22]. Subsequent experiments using microbial genetics revealed that *E.coli*-induced CRC in $Il10^{-/-}$ mice was dependent on the presence of the genotoxin colibactin [22]. Interestingly, the genomic island responsible for colibactin production is found at higher prevalence in CRC patients than non-CRC controls [22, 23]. Although the specific microorganism or group of microorganisms responsible for the development of human IBD or CRC has not been identified, it is generally recognized that microbial dysbiosis transfers CRC traits, at least in animal models [24, 25]. In addition, biotransformation of dietary products by various microbial enzymes, such as nitrate reductase, β-glucuronidase and alcohol dehydrogenease, generates various secondary metabolites (nitrite, hydrogen sulphide, acetaldehyde, etc.) with potential carcinogenic properties [26]. Consequently, although eubiosis is involved in intestinal homeostasis, dysbiosis and associated changes in microbial activities have the potential to foster development of CRC (Fig.1).

Microbes as beneficial factors against cancer

In less than a decade, the microbiome field has exploded and transcended many research disciplines, including molecular biology, immunology, development, neurology and cancer. At the intestinal level, it is clear that the microbiota has a broad impact on health and diseases. For example, *Bacteriodes fragilis* treatment can improve anxiety-related behavior and locomotive behavior, as well as barrier function in a murine model of autism spectrum disorders [27].

The concept that “good bacteria” could promote human health has been recognized for close to a century with the pioneer work of Eli Metchnikoff, which gave birth to the field of probiotic research. Not surprisingly, the efficacy of probiotics in modulating intestinal diseases has been investigated in various experimental models. *Echerichia coli* NISSLE 1917, a well documented probiotic used to alleviate diarrhea and intestinal inflammation in patients with IBD, has recently been shown to reduce tumor volume of breast tumor-bearing mice [28]. Others have shown that specific probiotics such as *Lactobacillus acidophilius* prevent cancer when administered before the onset of disease [29, 30]. Another study suggests that a mixture of probiotics containing *Lactobacilli* and *Bifidobacteria* enhances cancer development in mice by depleting potentially protective microbes, suggesting that manipulation of the microbiota with probiotics could result in deleterious effects [31]. In addition, some probiotic strains have been genetically engineered to modulate host response.

For example, IL-10 producing *Lactobacillus lactis* protected colitis-prone *Il10*$^{-/-}$ mice from the onset of inflammation, and subsequent clinical trials showed that this probiotic promoted remission in Crohn's disease patients paving the way for the use of microbes as drug-delivery vehicles [32]. *L. lactis* carrying human papilloma antigens and murine IL-12 induced an immune response and demonstrated anti-tumor effects in mice injected with TC-1 lung tumors [33]. In addition, lactobacillus acidophilus genetically engineered to lack the cell wall component lipoteichoic acid attenuated development of CRC in TS4Cre; APC^{lox468} mice [34]. The mechanisms by which probiotics impact intestinal biology are numerous and include reinforcement of the barrier function, changes in microbial composition, inactivation of carcinogens, reduced inflammation and increased apoptosis [35]. The reader is directed to recent reviews and perpectives in this field of research [30, 32, 35, 36].

The metabolic activity of the microbiome is substantial and some of these activities contribute to the metabolism of xenobiotics, a detoxification process beneficial for the host. As mentioned in a previous section, the metabolism of dietary components by gut microbes generates numerous beneficial, energy-rich nutrients, and essential micronutrients, (SCFA, vitamins, etc.) for the host. Similarly, detoxification and elimination of various pharmacological compounds by the microbiota is an essential process for host homeostasis [37]. The extent to which this microbial metabolic activity prevents cancer development is the subject of intense investigation.

Therefore, evidence for “local” effect (positive or negative) of intestinal microbiome on GI health has been firmly recognized. Intriguingly, two recent reports showed that microbial community disruption by means of antibiotic treatments impaired efficacy of chemotherapeutic drug treatment on distant tumors, implying a beneficial effect of microbes on cancer management [38, 39]. These findings indicate that, in addition to the “cancer promoting” ability of the microbiota as discussed above, the microbiota also performs “anti-carcinogenic” functions, at least in extra-intestinal tumors. These papers illustrate the far-reaching impact of the intestinal microbiota on host physiology, and highlight the need to fully comprehend the interaction between microbes, immune system and pharmaceutical intervention. Chemotherapeutic drugs such as cyclophosphamide and platinum-based agents have numerous adverse effects including enterotoxicity and neuropathy [40, 41], which compromise intestinal barrier integrity. In addition, chemotherapeutic agents may attenuate the immune response through direct T-lymphocyte toxicity, thereby promoting a state of immune-suppression. The combined gastrointestinal toxicity and immunosuppressive effect of chemotherapeutic drugs puts patients in danger of developing bacteremia or GI-associated sepsis. Consequently, the standard of care is to treat patients with antibiotics, especially those targeting gram-negative bacteria. Numerous studies have shown the potent effect of antibiotics on intestinal microbial ecosystem, where bacterial diversity and richness is severely attenuated [42, 43]. Although long-term or early antibiotic exposure has been linked to various health pathologies such as obesity and recurrent infection, the impact of antibiotic usage on chemotherapeutic drug efficacy was, until recently, unknown. This important question was tackled in a pair of studies by Iida et al. and Viaud et al. [38, 39]. In both studies, administration of antibiotics interfered with chemotherapeutic drug-induced

tumor regression in xenograft cancer models. For example, vancomycin abolished cyclophosphamide (CTX)-mediated reduction of MCA205 sarcomas in mice [39]. In the study by Iida et al. antibiotics alone had a negligible effect on tumor growth; however, the anti-tumor effects of CpG-oligodeoxynucleotides (CpG-ODN) in combination with an inhibitory interleukin-10 receptor antibody (αIL-10R/CpG) were attenuated in antibiotic-treated mice. In addition, GF animals subcutaneously injected with EL4 lymphomas were refractory to the anti-tumor effects of oxaliplatin, a chemotherapeutic drug that inhibits DNA synthesis. In contrast, SPF mice responded to the treatment and showed decreased tumor burden [38]. Similarly, Viaud et al. showed that CTX-mediated tumor size reduction was greater in SPF mice than in germ-free mice. As primary tumor load typically decreased in GF mice [14] it would be interesting to compare the rate of tumor growth between GF and SPF mice. Such an experiment may address the relationship between intestinal microbes and tumor burden at distant sites.

In both studies the authors emphasize the importance of the microbiota in contributing to the anti-cancer potential of chemotherapeutics. Iida et al. argue that the mechanism by which the microbiota increase the therapeutic efficacy of CpG-ODN is through enhanced myeloid cell-derived activities in tumors (Fig 2A). Importantly, abundance of Gram-positive microbes such as *Alistipes* (e.g *A.shahii*) and Gram-negative microbes such as *Ruminococcus*, positively correlated with TNF expression, while the presence of *Lactobacillus* was associated with ablated responses. Interestingly, *Lactobacillus reuteri*-specific immunoregulatory (rsiR) gene, which is implicated in histidine-histamine metabolism, suppresses TNF expression in human myeloid cells [44], suggesting that selective microbial activities could modulate host immune function and anti-tumor activities. Therefore, it is postulated that certain microbes 'prime' the immune responses elicited by the chemotherapy, thereby facilitating TNF-mediated anti-tumor response, while others may interfere with the efficacy of the chemotherapeutics. Interestingly, this mechanism is not shared by all chemotherapeutic drugs. For example, oxaliplatin-mediated tumor reduction is TNF-independent, and involved microbiota-induced expression of genes (e.g *Nox1*, *Cybb*) implicated in the generation of radical oxygen species (ROS) and cellular apoptosis [38]. The mechanism responsible for CTX-mediated anti-tumor activities is also different from CpG-ODN and oxaliplatin. Viaud et al. proposed that CTX administration compromised intestinal barrier integrity and rapidly (<48h) caused translocation of mucosal-associated Gram-positive bacteria (*Lactobacillus* and *Enterococcus*) into secondary lymphoid organs, which drove the differentiation of naïve T-cells into anti-cancer, 'pathogenic' T_H17 cells and T_H1 cells (Fig. 2B)[39]. This CTX mediated bacterial translocation has repercussions on microbial composition, as witnessed by the development of microbial dysbiosis one week post-treatment. Remarkably, CTX-mediated tumor regression was rescued in antibiotic-treated mice with the adoptive transfer of pTH17 cells from non-treated mice. Although the effects of dysbiosis on tumor regression were not directly addressed, the authors observe a decrease in *Lactobacillus* in the small bowel, but an increase in the spleen, which correlates with a T_H17 signature after one week. These findings demonstrate that bacteria modulate chemotherapeutic drug efficacy through various mechanisms.

These findings complement recent findings demonstrating that the toxicity associated with these agents seems to be related to microbial activities. For example, while CPT-11 is detoxified in the liver, microbial β-glucuronidases reverse the conjugation and reactivate the drug into its toxic form, causing GI injury and diarrhea. Remarkably, small molecule inhibitors targeting microbial β-glucouronidase were shown to prevent the deconjugation of CPT-11, and attenuate the associated toxicity for the intestine [37]. Together with the pro-carcinogenic activities of certain microbial communities, these findings illustrate the complex role-play by bacteria in carcinogenesis.

Conclusions and outlook

The interplay between the intestinal microbiota and carcinogenesis appears complex, having both promoting and protecting effects (Fig. 3). Clearly, understanding the various elements implicated in this complex relationship could provide significant advancement for cancer detection and management. Based on the recent studies by Viaud [39] and Iida [38], the microbiota may even influence cancer treatment efficacy, adding a supplemental layer of complexity to the role of microorganisms in cancer (Fig. 3). Therefore, microbiota research offers a spectrum of possibilities of therapeutic and translational impact in cancer patients. Since microbial dysbiosis is associated with different forms of cancer, especially CRC, research dedicated to the generation of microbial biomarkers to monitor cancer development/progression and/or response to treatment should be considered. Although the work of Viaud and Iida suggests that bacteria could be utilized as a tool to promote/enhance chemotherapeutic drug treatment, a series of questions must be addressed before exploring this possibility further. First, these findings suggest that antibiotic treatment negatively impacts chemotherapeutic drug efficacy. Antibiotics are frequently administered to cancer patients as a preventative measure to decrease infection risk associated with both surgery and chemotherapy. Thus, prospective studies should be conducted to address the potential inhibitory effect of antibiotics on chemotherapeutic drug-mediated tumor regression. These studies will need to be carefully controlled, because antibiotics also impact the immune system, for example, by decreasing the number of Peyer's patches [45]. In addition, cyclophosphamide potently inhibits humoral immune responses and reduces splenic, thymic and peripheral lymphocytes [40]. The extent to which these immunosuppressive functions of antibiotics and chemotherapeutics interfere with the immune responses required for anti-tumor effects remains to be seen.

More investigations are required to identify microorganisms with the best immunological potential, a characteristic essential for enhancing chemotherapeutic drug efficacy. Similarly, understanding which microorganisms interfere with drug efficacy would be of prime importance for cancer therapy. Armed with this knowledge, patients' microbiota could potentially be profiled for presence of microorganisms with the best “immunological” potential, hence establishing optimal anti-cancer drug responders. The generation of microbial signature could allow an optimal “match” of patients with chemotherapeutic drugs, essentially a form of personalized medicine based on the microbiota. For example, while some lactobacilli contribute to the generation of anti-tumor pTh17 cells in CTX-treated mice [39], the same genus attenuates CpG-ODN induced myeloid-derived TNF production [38].

These studies have paved the way for future work deciphering the complex and wide spectrum activity of the microbiota on carcinogenesis, ranging from promoting, prevention, and treatment. As our understanding of the interplay between bacteria and cancer progresses, novel paradigms and therapeutic targets will likely emerge.

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Abbreviations

CRC	colorectal cancer
CTX	cyclophosphamide
IBD	inflammatory bowel disease
SCFA	short-chain fatty acid

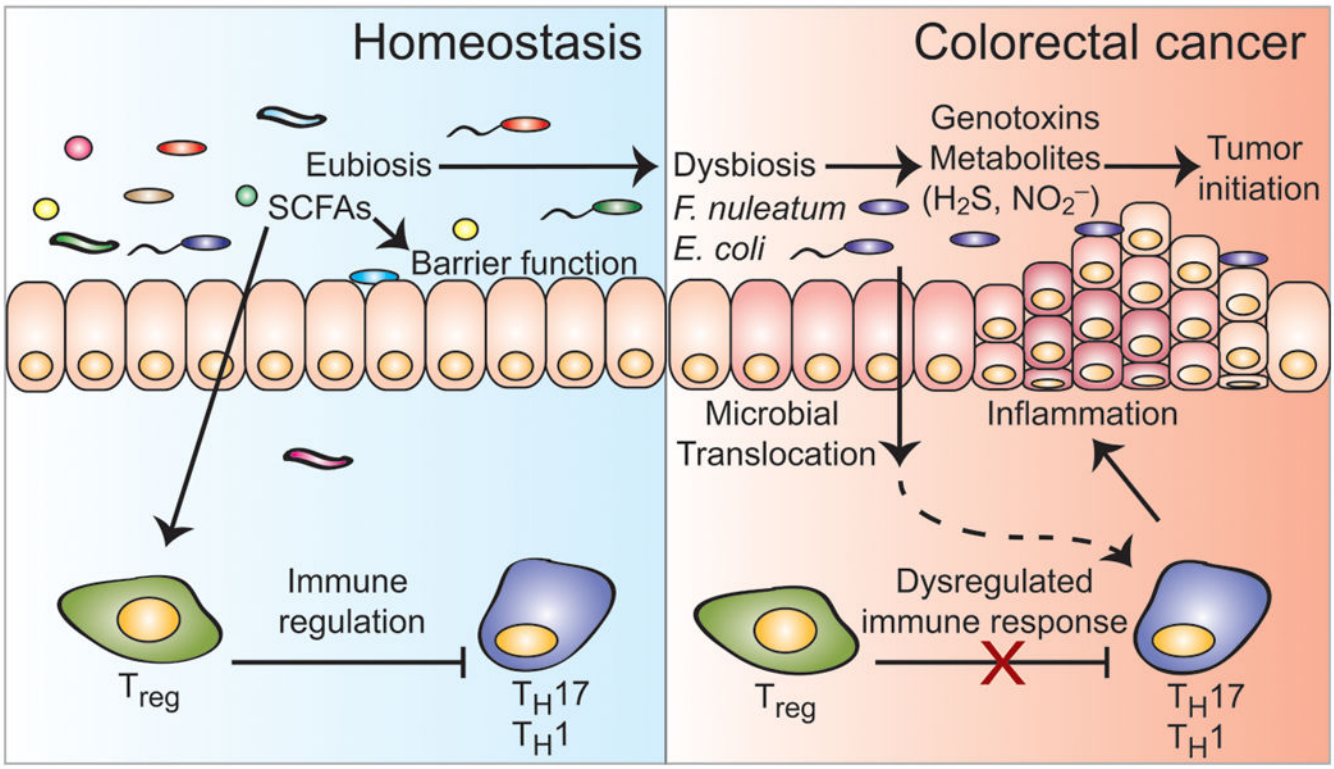

Figure 1.

At eubiosis stage, the intestinal epithelium contains a rich and diverse biota that promotes the barrier function. Short-chain fatty acids (SCFAs), such as butyrate and propionate promote the differentiation of regulatory T-cells (Treg), thereby down-regulating inflammatory responses from effector T-cells (T_H17 and T_H1) cells, and maintaining homeostasis. Events that disrupt microbial community lead to a state of dysbiosis and loss of homeostasis. Microbial dysbiosis favors the production of genotoxins and metabolites associated with carcinogenesis. Microbes such as *F. Nucleatum* and *E. coli* are associated with colorectal cancer. Dysregulated immune responses cause inflammation and epithelial disruption, which further enhance microbial translocation, exacerbating immune activation and promoting carcinogenesis.

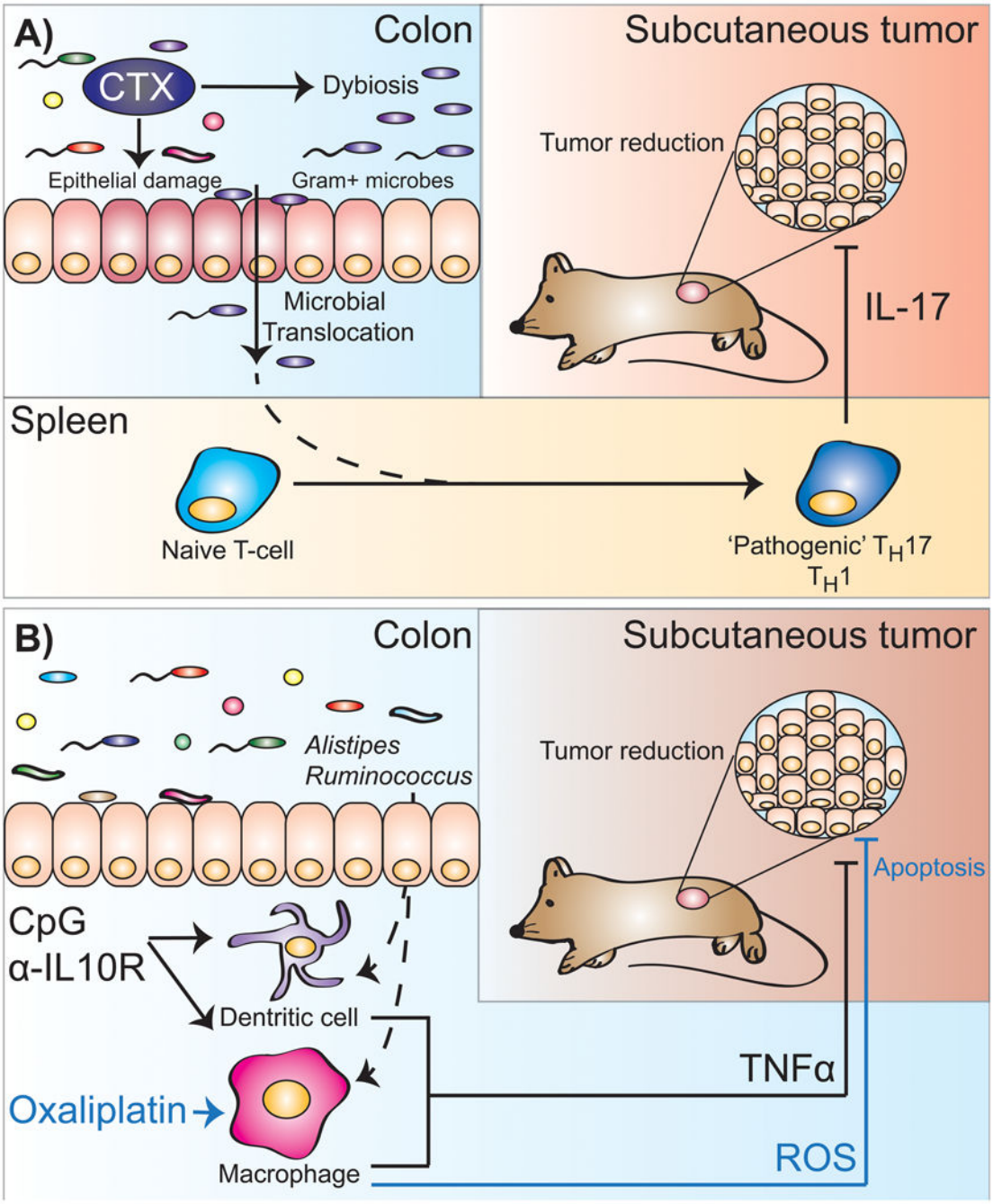

Figure 2.

Microbes promote the therapeutic efficacy of chemotherapeutic drugs, reducing the size of extra-intestinal tumors. **A:** Cyclophosphamide (CTX) damages the epithelial layer, resulting in the translocation of Gram + bacteria to secondary lymphoid tissues such as the spleen, with subsequent differentiation of naïve T cells into pathogenic anti-tumor T_H17 and T_H1 cells. **B:** The chemotherapeutic efficacy of the anticancer regimen (CpG-ODN/anti-IL10 antibodies) is increased by the gut microbiota, in particular microbes belonging to the genera *Alistipes* and *Ruminococcus*. These microbes 'prime' myeloid cell responses resulting in a

potent TNFα-mediated response. Oxaliplatin causes apoptosis of tumor cells through the generation of radical oxygen species.

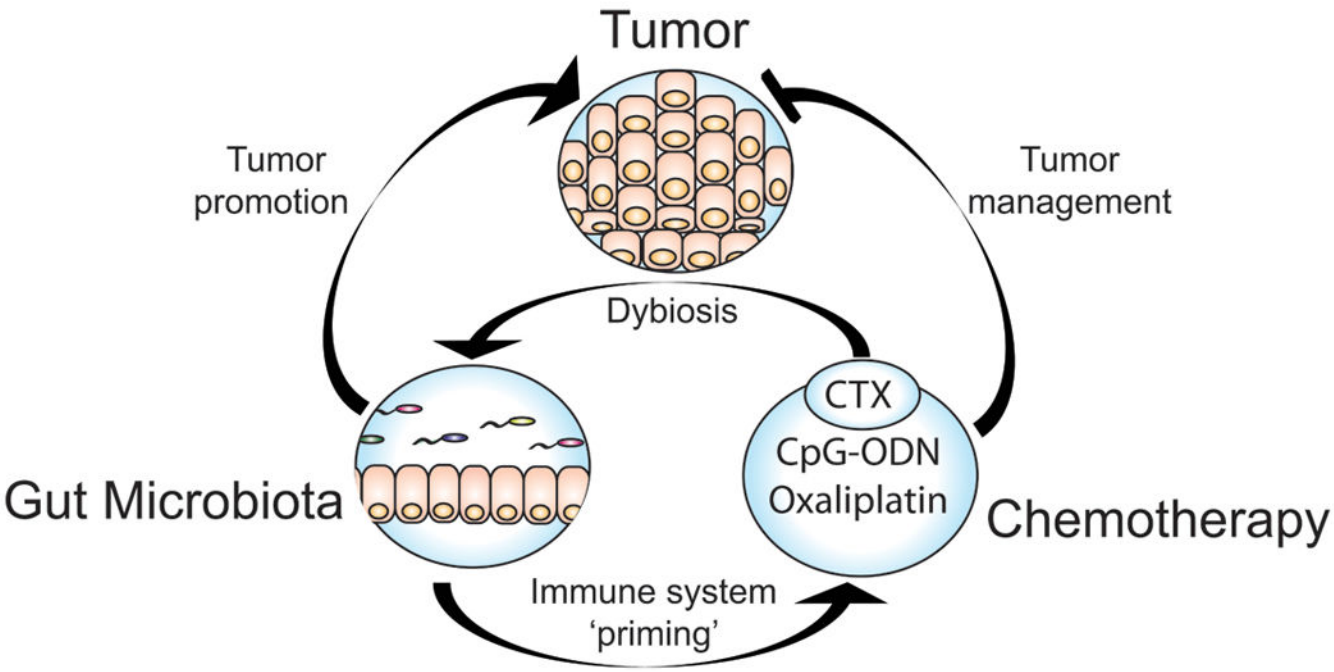

Figure 3.

Intestinal microbial composition modulates tumor development. Dysbiotic intestinal microbiome containing tumor-promoting microbes fosters cancer development (e.g. CRC). On the other hand, the microbiota is essential for the therapeutic efficacy of chemotherapeutic drugs, either by 'priming' the anti-tumor immune responses (CHX, CpG-ODN) or by facilitating anti-tumor toxicity (oxaliplatin).