Journal of Cancer Research and Clinical Oncology (2019) 145:49–63
https://doi.org/10.1007/s00432-018-2816-0

REVIEW – CANCER RESEARCH

Microbiota in cancer development and treatment

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Received: 11 August 2018 / Accepted: 5 December 2018 / Published online: 12 December 2018

Abstract

Purpose Human microbiota comprises of a variety of organisms ranging from bacterial species to viruses, fungi, and protozoa which are present on the epidermal and mucosal barriers of the body. It plays a key role in health and survival of the host by regulation of the systemic functions. Its apparent functions in modulation of the host immune system, inducing carcinogenesis and regulation of the response to the cancer therapy through a variety of mechanisms such as bacterial dysbiosis, production of genotoxins, pathobionts, and disruption of the host metabolism are increasingly becoming evident.

Methods Different electronic databases such as PubMed, Google Scholar, and Web of Science were searched for relevant literature which has been reviewed in this article.

Results Characterization of the microbiome particularly gut microbiota, understanding of the host–microbiota interactions, and its potential for therapeutic exploitation are necessary for the development of novel anticancer therapeutic strategies with better efficacy and lowered off-target side effects.

Conclusion In this review, the role of microbiota is explained in carcinogenesis, mechanisms of microbiota-mediated carcinogenesis, and role of gut microbiota in modulation of cancer therapy.

Keywords Microbiome · Gut microbiota · Carcinogenesis · Cancer therapy

Introduction

The human microbiota comprises of several types of over one hundred trillion organisms including bacteria, viruses, fungi, and protozoans that are primarily inhabited on the epithelial surface of human body. Human gut is the major contributor to the human microbiome. It has largest number of bacteria and is very diverse with respect to the other areas of human body. It provides nutrient rich and protective conditions to resident microbiota. Whilst, the gut microbiota benefits human body by playing a key role in the production of short chain fatty acids (SCFAs) from dietary fiber, synthesis of vitamin B and vitamin K, metabolism of several compounds such as sterols and xenobiotics, and regulation of immune functions (Clarke et al. 2014; Quigley 2013; Shen and Wong 2016). However, its role in several diseases such as cancer, liver disease, obesity, and neuropsychiatric disorders has also been reported (Boulangé et al. 2016; Minemura and Shimizu 2015; Wang and Kasper 2014; Zitvogel et al. 2015). Host immune system tolerates the human microbiota while safeguarding against the invading pathogenic microbes (Zitvogel et al. 2015). Particularly, it plays a key role in cancer initiation, development, and its response to cancer therapy (Fig. 1; Tables 1, 2).

Living organisms which are raised in controlled environment that prevents the growth of microbiota in them; also known as germ free organisms, have several poorly developed physiological conditions such as innate immunity

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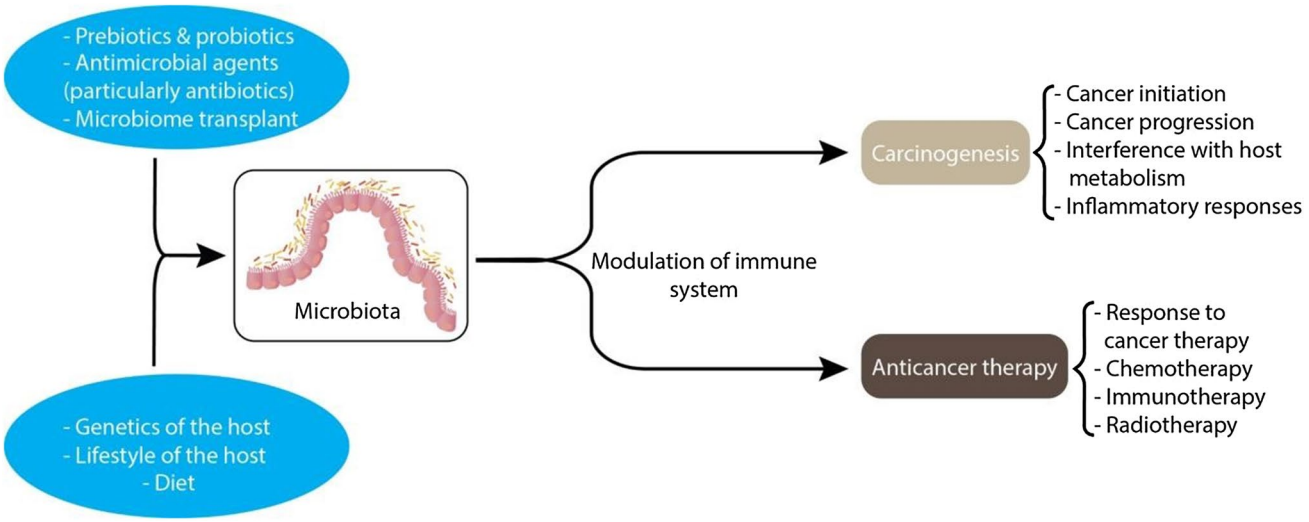

Fig. 1 Microbiota and Carcinogenesis. Microbiota plays a key role in maintenance of host physiological functions as well as disease development through interference with the immune system. When disrupted, i.e., dysbiosis in microbiota, can lead to cancer development. Furthermore, several factors such as intake of antibiotics, defined transplant of microbiome, as well as lifestyle of the host modulates carcinogenesis and the response to cancer therapy

Table 1 Bacteria associated with carcinogenesis

Bacterium specie	Type of cancer	Type of association	Mechanism in Carcinogenesis	References
Fusobacterium nucleatum	CRC	Enriched	Instigation of NF-κβ signaling cascade for stimulation of Wnt signaling pathway	Mima et al. (2015)
Escherichia coli NC101	CRC	Causative	Production of genotoxins	Taieb et al. (2016)
Streptococcus gallolyticus	CRC	Causative	Promotion of inflammatory responses via IL-1, IL-8, and COX-2	Abdulamir et al. (2010)
Bacteroides fragilis	CRC	Causative	Production of toxins, promotion of breakdown of E-cadherin	Boleij et al. (2014)
Helicobacter pylori	CRC	Enriched	Production of Vacuolating cytotoxin A (VacA)	Epplein et al. (2013)
Salmonella typhi	Gall bladder cancer	Causative	Chronic typhoid carriage	Nath et al. (1997)
Helicobacter pylori	Gall bladder cancer	Causative	Aggravation of mucosal lesions	De Martel et al. (2009)
Chlamydia pneumonia	MALT	Causative	Advanced stage infection	Chanudet et al. (2007)
Chlamydia psittaci	MALT	Causative	Advanced stage infection	Chanudet et al. (2007)
Chlamydia psittaci	Ocular Adnexa MALT cancer	Causative	Advanced stage infection	Chanudet et al. (2007)
Mycoplasma sp.	Ovarian carcinoma	Causative	Controversial	Chan et al. (1996)
Chlamydia pneumonia	Ovarian carcinoma	Enriched	Advanced stage infection	Shanmughapriya et al. (2012)
Prevotella sp.	Oral cancer	Enriched	Controversial	Hooper et al. (2007)
Bacillus sp.	Lung carcinoma	Enriched	Production of toxins	Apostolou et al. (2011)
Mycoplasma sp.	Lung carcinoma	Causative	Production of ROS leading to DNA damage	Apostolou et al. (2011)
Staphylococcus epidermis	Lung carcinoma	Enriched	Stimulation of cellular proliferation in lung cancer tumors by lipoteichoic acids	Apostolou et al. (2011)

which makes them prone to pathogen-mediated infections (Roy and Trinchieri 2017). However, germ free organisms fed with nutritious components that are normally supplied by gut microbiota live significantly longer than the conventional ones (Roy and Trinchieri 2017). The underlying mechanism through which commensal microbiota regulates systemic

Table 2 Bacterial genotoxins and metabolites associated with cancer

Toxin/Metabolite	Mode of action	Bacterial specie	References
FadA	Adhesin which is located on the surface of bacterial specie activates β-catenin and promotes inflammatory responses	*Fusobacterium nucleatum*	Garrett (2015)
CagA	Increases cellular proliferation by activating β-catenin	*Helicobacter pylori*	Garrett (2015)
Trimethylamine-N-oxide (TMAO)	Utilization of L-carnitine for production of TMAO	*Clostridium* sp.	Faith et al. (2013)
Cytolethal distending toxin (Cdt)	Promotes genomic instability	*Epsilonproteobacteria* sp.	Gagnière et al. (2016)
Btf	Induces oxidative DNA damage by increasing ROS levels	*Bacteroides fragilis*	Boleij et al. (2014)
Butyrate	Promotion of cellular proliferation and induction of apoptotic cell death	*Bifidobacterium* sp.	Belcheva et al. (2014)
Deoxycholic acid	Activation of β-catenin mediated signaling cascades	*Clostridium* sp.	Ha and Park (2010)
Fragilysin	Activation of β-catenin mediated signaling cascades	*Bacteroides fragilis*	Sears et al. (1995)
Lithocholic acid	Induction of tumor metastasis	*Bacteroides fragilis*	Baek et al. (2010)

functions is less understood as compared to those of localized functions (Belkaid and Naik 2013).

Several risk factors including pathogen associated infections have been linked with human cancers (Perez-Chanona and Trinchieri 2016). Chronic infections lead to various types of cancers; with about 18% of the human cancers directly caused by infectious agents through well-understood molecular mechanisms. Amongst several microbes including oncogenic viruses, infection with only one bacterium *Helicobacter pylori* leads to increased risk of development of stomach cancer (Perez-Chanona and Trinchieri 2016). However, recent studies have shown that pathogens as well as the commensal microbiota also influences several diseases; thereby acting as causative agents. When the surrounding environment of human gut microbiota is disturbed, several species of the commensal microbiota such as *Clostridium difficile* and vancomycin resistant *Enterococci* (VRE) become pathogenic (Roy and Trinchieri 2017). Human microbiota that accompanies gut and epithelial surface of human body influences cancer initiation and progression, and the effect of cancer treatment on tumor cells by interfering with the systemic metabolism, immune system, and inflammation. Several factors including genetics of the host and environmental conditions such as diet affect the diversity of microbiota, ultimately modulating carcinogenesis and cancer therapy (Raza et al. 2017; Roy and Trinchieri 2017). In this review, we target the mechanisms of microbiota induced carcinogenesis and the regulation of cancer therapy by microbiota.

Microbiota and carcinogenesis

Microbiota and host, i.e., humans have coevolved resulting in a mutualistic relationship that benefits both microbiota and the host. Disruption of the host pathways that regulate the homeostasis inside the host may lead to increase in risk of development of certain diseases (Consortium 2012). As gastrointestinal microbiota is the major constituent of the human microbiome, it has strong influence on the health of host and has been well studied for the understanding of host–microbiota relationship and development of disease. Skin and vagina are other organs of human body with distinct microbiota (Consortium 2012). Variation in the diversity and relationship of the microbiome and organs suggest that the modulation of inflammation, cancer initiation and development, and its response to cancer therapy are different with respect to each organ. The number of microbes and their diversity in microbiome show discrepancy in various sites within an organ. Moreover, the host microbiome also varies from individual to individual being indicated as a potent factor for the development of specific diseases including cancer (Consortium 2012). Several studies have indicated that despite lacking microbiome, several organs of human body are prone to carcinogenesis due to exposure to microorganism associated molecular patterns (MAMPS) and various metabolic products released by bacteria (Dapito et al. 2012; Schwabe and Jobin 2013a; Yoshimoto et al. 2013b). These metabolites reach to the specific organs from gut via anatomical connections.

Numerous bacterial species have been provenly linked with carcinogenesis directly or indirectly. Based on quantitative polymerase chain reaction (PCR) technique, 16 s rDNA sequencing, and analysis of fluorescence in situ hybridization (FISH), elevated levels of *Fusobacterium* spp. Especially *F. nucleatum* have been detected in colorectal adenomas and cancer (Castellarin 2012 #207). Its DNA is prevalently found in tumor cells and is correlated with lymph node metastasis. It promotes carcinogenesis by stimulating the Wnt signaling cascade in colorectal carcinoma (Mima 2015 #208). Probiotic bacterium species especially *Lactobacillus* and *Bifidobacterium* genera exert beneficial

impacts on the host. Immune responses have been shown to be boosted against numerous types of cancers after oral administration of *Bifidobacterium* (Sivan et al. 2015 #209). It is also proposed to enhance the efficacy of chemotherapeutic drugs. Meanwhile, *lactobacillus* decreases the production of beta-catenin and promotes expression of p53 (Gamallat et al. 2016 #210). *Lactobacillus rhamnosus* GG has been linked with enhancement of function of epithelial barrier in the intestine in TLR2/COX2 dependent method. However, the underlying mechanism is poorly understood (Dong et al. 2012 #211}.

Several studies conducted on germ-free organisms have proved that microbiota promotes carcinogenesis in various organs such as lungs, skin, and breast (Dapito et al. 2012; Schwabe and Jobin 2013a). Likewise, risk of developing cancer decreases in mice that have intestinal microbiota depleted by antibiotics (Chen et al. 2008; Klimesova et al. 2013; Yu et al. 2010). Besides the tumor-inducing effects of microbiota, anticancer effects have also been reported (Schwabe and Jobin 2013a). For instance, toll-like receptor (TRL) agonists promote antitumor effects of microbiota, as the innate immune system may lead to activation of anticancer responses (Garaude et al. 2012; Pradere et al. 2014). Nevertheless, besides TLR- and NOD-like receptors (NLR)-based treatments, the immune responses triggered by microbiota are insufficient for inducing anticancer activity. Conversely, it usually promotes disease-inducing immune responses (Pradere et al. 2014). To conclude, increasing evidences from studies conducted on animal models and patients indicate the pro-cancer properties of microbiota that affect several organs of the host, particularly those which have diverse microbiota or are exposed to MAMPs. However, the molecular and cellular mechanisms of microbiota-induced carcinogenesis differ significantly in different organs. The various mechanisms through which microbiota is involved in carcinogenesis and response to cancer therapy as described in this section (Fig. 2).

Microbiota dysbiosis and carcinogenesis

Disruption of human microbiota is referred to as dysbiosis. It is characterized by lowered diversity of microbes in the gut and is linked with mutations in the host genes which affect the immune system by interfering with the innate immunity in the host (Hold et al. 2014; Sartor and Mazmanian 2012). Significant variation occurs in diversity of microbiota in different organs of human body. Microbiota as well as the metagenome is affected by diet change, antibiotics, xenobiotics, host immune system, and infectious diseases (Arthur et al. 2012; Holmes et al. 2012; Schwabe and Jobin 2013a).

The association of intra-abdominal infections with increased risk of development of colorectal cancer (CRC) accentuate the clinical significance of dysbiosis of human microbiome and carcinogenesis. Alterations in the composition of microbiota directly modulates the risk of development of CRC in animal models with genetic and mutagen induced carcinogenesis (Arthur et al. 2012; Bonnet et al. 2014; Zhan et al. 2013). Furthermore, intestinal epithelial cells (IECs) are targeted by metabolites of intestinal microbiota which either induces tumorigenesis; as in case of *Bacteroides fragilis*, or inhibits it; for instance, SCFAs (Louis et al. 2014a).

Manipulation of the gut microbiome of experimental mice models including germ-free, cohoused, mice with microbiota depleted after treatment with antibiotics, and gnotobiotic models has revealed its involvement in CRC and hepatocellular carcinoma (HCC) (Consortium 2012; Dapito et al. 2012; Grivennikov et al. 2012; Yoshimoto et al. 2013a; Zhang et al. 2012). Meanwhile, studies on *Nod2*$^{-/-}$, *NIrp6*$^{-/-}$, and *Asc*$^{-/-}$ experimental mice models indicate that dysbiosis promotes carcinogenesis (Couturier-Maillard et al. 2013; Hu et al. 2013). On the other hand, obesity that leads to dysbiosis is also a risk factor for carcinogenesis and is linked with dysmetabolism in humans (Cotillard et al. 2013; Le Chatelier et al. 2013; Schwabe and Jobin 2013b). For instance, in case of HCC, obesity increases the growth rate of *Clostridia* sp. that produces deoxycholic acid (DCA) which in turn promotes HCC (Yoshimoto et al. 2013a). However, direct evidences of role of *Clostridia* sp. in carcinogenesis in certain experimental mice models are still missing. Similarly, increased biosynthesis of taurocholic acid by dietary fats in colon promotes the growth of *Bilophila wadsworthia*; a pathobiont (Devkota et al. 2012). However, a well characterized direct association between obesity-promoted dysbiosis and CRC is still lacking.

Dysbiosis in mucosal sections of patients with CRC has been reported in several studies with a significant correlation between all of them (Chen et al. 2012; Sanapareddy et al. 2012; Sobhani et al. 2011; Wang et al. 2012a). Nevertheless, *Fusobacterium nucleatum* can be regarded as a potential microbial specie for CRC susceptibility (Kostic et al. 2012, 2013). Its prevalence is lesser in healthy individuals as compare to the microbiota of patients with Crohn's disease (Allen-Vercoe et al. 2011). It also promotes intestinal carcinoma in *Apc*$^{Min/+}$ mice models (Kostic et al. 2013). The underlying mechanism of *F. nucleatum* induced carcinogenesis indicates that *F. nucleatum* adhesin FadA attaches with E cadherin and leads to activation of β catenin in CRC tumors which in turn promotes inflammation and tumor formation (Rubinstein et al. 2013). Notably, FadA is expressed with significant high rates in human CRC samples (Rubinstein et al. 2013). Increased redundancy of microbiota at metagenomic level suggests the possibility of promotion of carcinogenesis by alterations in community richness of microbes and their functions, and by various bacterial species through similar mechanisms (Huttenhower et al. 2012).

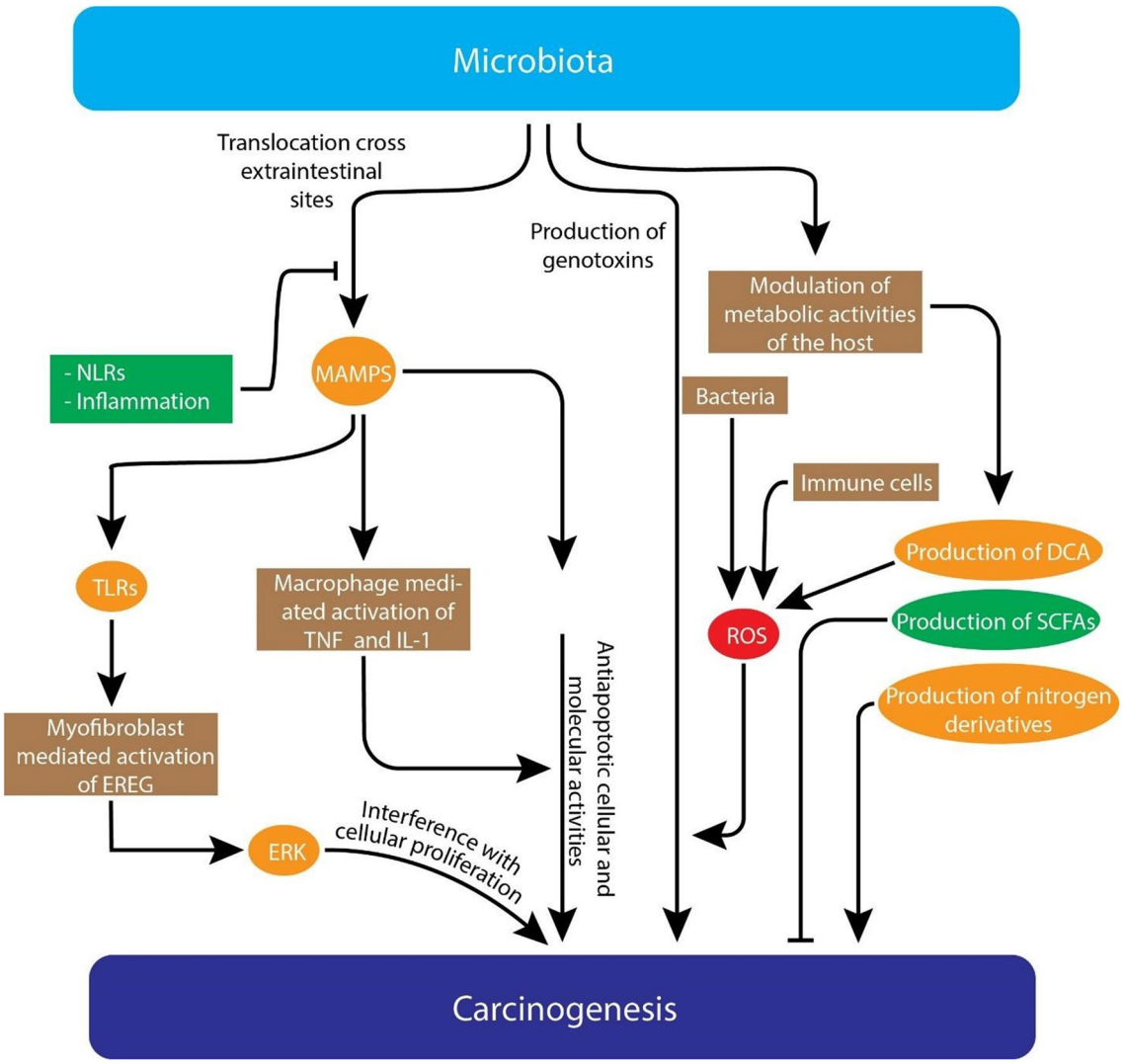

Fig. 2 Mechanism of modulation of carcinogenesis by microbiota. Translocation of microbiota across extraintestinal sites leads to induction of inflammatory responses that are activated through microorganism-associated molecular patterns (MAMPS) which subsequently activate TLRs leading to several on-site and off-site effects that promote carcinogenesis. Meanwhile, genotoxicity induced by the genotoxins and ROS produced by bacteria also lead to development of cancer. Microbiota also interferes with the metabolic activities of the host that can result in either suppression of carcinogenesis by SCFAs or promotion by cancer-inducers

Furthermore, horizontal gene transfer (HGT) between pathogenic microbes and commensal microbiota, specifically in aspect of pathogen-promoted inflammatory responses, indicates the transfer of oncogenes between bacterial species (Stecher et al. 2012).

Dysbiosis in gut microbiota plays a key role in the onset of several types of cancers other than CRC. Experimental findings from studies conducted on alterations of gut microbiota reveal that it affects the initiation and progression of breast and HCC (Louis et al. 2014b; Yoshimoto et al. 2013a; Zitvogel et al. 2015). There is a significant linkage between these findings and the results of epidemiological experiments carried out to analyze the linkage between dysbiosis and its consequent results; particularly after continuous intake of antibiotics, and an elevated occurrence of extracolonic neoplasms counting breast carcinoma. These results also depict the systematic distribution of microbiota and its metabolites in perspective of immune responses that compromise the intestinal barrier (Zitvogel et al. 2015).

The main pathways that promote dysbiosis and disruption of the balanced microbial community richness are poorly understood. Host-promoted inflammation and immune responses are key factors that determine the composition of microbial richness in microbiota and may lead to dysbiosis if altered, as studied in several experimental mice models (Arthur et al. 2012; Couturier-Maillard et al. 2013; Hu et al. 2013). Besides modulation of microbial community richness by innate immune responses, several mediators

of inflammation may also form environment favorable for growth of specific bacterial species. Inflammation affects the biosynthesis of several metabolites such as nitrate which is produced from reactions of inducible-nitric oxide synthase (iNOS). Nitrate may act as an energy provider for facultative anaerobic microorganisms which enables them to survive in microbial community rich with obligate anaerobic microorganisms (Winter et al. 2013). Therefore, *Enterobacteriaceae* spp. has been found in experimental models and patients with inflammatory diseases (Lupp et al. 2007; Morgan et al. 2012; Vijay-Kumar et al. 2010). Likewise, induction of stress-response genes in response to inflammation in bacteria could be a risk factor for development of bacterial survival and adaptability. For instance, isolates of *Escherichia coli* from experimental mice model $I110^{-/-}$of inflammatory disease had elevated levels of a variety of heat shock proteins that protect the host from oxidative damage (Patwa et al. 2011). Finally, promotion of dysbiosis via exertion of dominating effects by low-abundance microbes has also been suggested (Hajishengallis et al. 2012).

Pathogenic microbes and carcinogenesis

Infection with numerous bacterial species leads to carcinogenesis. As microbiota is present in the tumor microenvironment, it may actively contribute to the development of gastrointestinal tract malignant carcinomas.

Gastric cancer is an elusive example of bacteria-promoted cancer which is caused by *Helicobacter pylori*; declared by International Agency for Research on Cancer (IARC) a major cause of cancer mortality worldwide (Roy and Trinchieri 2017). Although it has been classified as a carcinogen, yet a complex microbiota is required for development of gastric cancer. For instance, a study on hypergastrinaemic transgenic experimental mice model revealed that the lesser tumors were developed in models with *H. pylori* only when compared than pathogen-free models (Lofgren et al. 2011). This is because of the elevated metabolism of dietary nitrogen-derivatives into carcinogens by overgrown microbial communities of stomach due to *H. pylori*-promoted gastric atrophy and hypochlorhydria (Lofgren et al. 2011). Conversely, it reduces the risk of development of oesophageal adenocarcinoma in humans; indicating the tissue-specific anticarcinogenic effects of bacterial microbiota (Islami and Kamangar 2008).

Likewise, several other types of cancers are promoted by specific bacterial pathogens. Gall bladder cancer is caused by infection with *Salmonella enterica* subsp. *Enterica* serovar Typhi (Caygill et al. 1994; Roy and Trinchieri 2017). Activity of adaptive immunity in response to infection with specific pathogens lead to development of mucosa-associated lymphoid tissue (MALT) lymphoma. *H. pylori* specific immune responses such as expression of *H. pylori* antigen specific *T* helper (T_H) cells is the main symptom of gastric MALT lymphoma (Bayerdörffer et al. 1995). Further, infection with *Campylobacter jejuni* and *Chlamydia psittaci* is also linked with certain lymphomas (Ferreri et al. 2012; Lecuit et al. 2004; Senff et al. 2008).

Association of microbial toxins and virulence factors with carcinogenesis

Certain bacterial species can contribute to chronic inflammatory disease consequently resulting in increased production of reactive oxygen species (ROS) which ultimately mediates genotoxicity. Whilst, they can also modulate carcinogenesis via production of specific bacterial toxins that can induce DNA damage. Due to alterations in the epithelial barrier, bacterial species can cross it and can deliver their toxins easily to the host cells due to direct contact with them. Various bacterial toxins such as *Bacillus fragilis* toxin, colibactin, and cytolethal distending toxin (CDT) can affect cellular responses that are involved in carcinogenesis; specifically, those against DNA damage (Arthur et al. 2012; Cuevas-Ramos et al. 2010; Nešić et al. 2004; Travaglione et al. 2008; Wu et al. 2009). Nevertheless, CDT and colibactin can induce genomic instability and are referred to as genotoxins (Cuevas-Ramos et al. 2010; Nešić et al. 2004). They promote double stranded DNA (dsDNA) damage cellular responses such as ataxia telangiectasia mutated (ATM)-signaling cascades resulting in G2/M cell cycle disruption. CDT is a Gram-negative bacteria toxin which is produced by all microbes such as *E. coli, Salmonella typhi*, and *H. pylori* that are responsible for promotion of carcinogenesis in various organs of gastrointestinal tract (Smith and Bayles 2006). Once infected, CdtA and CdtC aid in attachment of the bacterium with the host cells by forming an anchor between them and enabling the transport of CdtB which induces DNA damage in the nucleus (Nešić et al. 2004). Mutations that alter the structural configuration of active site of CdtB, which is homolog of DNase I sites, depletes cellular responses due to genomic instability and DNA damage in vitro together with cell cycle disruption (Roy and Trinchieri 2017). CDT-induced DNase activity may also be responsible for tumorigenic capability of CDT-producing bacteria such as *Helicobacter cinaedi*. CdtB mutants were unable to promote intestinal hyperplasia in experimental mice models with no NF-κβ, Nfkb1, and one allele of Rela, and were also unable to induce dysplasia in Il10–/– experimental mouse models (Fox et al. 2004; Shen et al. 2009).

Colibactin is another genotoxin which is encoded by polyketide synthase (pks). *Pks* is mainly expressed in *Enterobacteriaceae* with dominancy in *E. coli* (Nougayrède et al. 2006). *E. coli* NC101 *pks* was associated with promotion of CRC in experimental mice Il10–/–. Similarly, two bacterial species *Proteus mirabilis* and *Klebsiella pneumoniae* contain

pks and can induce colitis in immunodeficient mouse models with depleted levels of expression of TBX21 and recombination-activation gene 2 (RAG2) (Garrett et al. 2010; Putze et al. 2009). However, their role in CRC promotion alongside colibactin remains unclear. Purification of colibactin has not been reported yet, however, results from various studies show that pks and non-ribosomal peptide synthetase (NRPS) are necessary to produce active colibactin. *E. coli* with pks can induce dsDNA breaks and related ATM-promoted responses against DNA damage and disruption of cell cycle (Nougayrède et al. 2006). Furthermore, numerous metabolic products of bacteria such as hydrogen sulfide may induce genomic instability. For instance, superoxide radicals produced by *Enterococcus faecalis* can induce dsDNA breaks leading to promotion of CRC in Il10–/– mouse (Carbonero et al. 2012; Huycke and Gaskins 2004; Wang and Huycke 2007). Conversely, *E. faecalis* mutants such as ΔmenB which cannot produce superoxide radicals could not induce carcinogenesis in Il10–/– mouse as compared to the mouse with wild type of *E. faecalis* (Wang et al. 2012b). Sulphate-metabolizing microorganisms such as *Fusobacteria*; which are associated with CRC development, and delta proteobacteria produce hydrogen sulphide which is genotoxic in nature (Attene-Ramos et al. 2006; Castellarin et al. 2012; Kostic et al. 2012, 2013). Elimination of these genotoxics by host or microorganisms may affect the cellular homeostasis and tumorigenesis.

Disease-inducing and pro-cancer properties of pathogenic microorganisms rely on virulence factors. For example, elevated levels of inflammatory disease and carcinogenesis in *H. pylori* producing cytotoxin-associated gene A (CagA) (Fox and Wang 2007). Virulence factors utilize specific signaling cascades of the host to activate protumor signaling pathways such as tyrosine phosphatase SHP2 (PTPN11). For instance, they promote gastric cancer in transgenic mice models with active CagA but not in mice with CagA with resistance to phosphorylation (Ohnishi et al. 2008). Similarly, *F. nucleatum* can induce CRC by activation of β-catenin signaling pathway via interaction with E cadherin (Han et al. 2005; Rubinstein et al. 2013). Virulence factors of several other bacterial species of microbiota may promote carcinogenesis. However, further studies on this aspect are needed.

Microbiota mediated metabolism and carcinogenesis

Enzymes secreted by bacterial species of human microbiota play a key role in human metabolism (Gill et al. 2006). Interestingly, bacterial metagenome is complex and diverse in perspective of genes for biosynthesis and catabolism of various compounds (Gill et al. 2006; Philipp 2011). These metabolic processes modulated by human microbiota affect tumorigenesis by interfering with obesity-promoted inflammatory disease, biosynthesis and detoxification of various compounds such as nitrogen-derivatives, acetaldehyde, phytochemicals, and pro-cancer secondary bile acids.

Hydrolase is utilized by gut microbiota to regulate the metabolism of bile. It largely interferes with the composition of bile by removing polar groups from it enabling the gut microbes to use it as energy source (Philipp 2011). Gut microbiota richness and the production levels of DCA is increased by fat rich diet. Intriguingly, DCA supplementation promotes HCC whilst depletion of bacteria producing DCA decreases it (Yoshimoto et al. 2013a). Furthermore, DCA is also a risk factor for development of colon and oesophageal cancer suggesting the role of microbiota in modulation of these cancers via DCA generation, specifically in the aspect of obesity (Bernstein et al. 2011; Quante et al. 2012; Yoshimoto et al. 2013a).

Production of SCFAs via microbiota-derived metabolism of carbohydrates may benefit the host (Nyangale et al. 2012). In contrast, protein metabolism may lead to production of pro-metabolites such as nitrogen derivatives including ammonia and nitrosamines, and sulfur derivatives (Alam et al. 1971; Carbonero et al. 2012; Windey et al. 2012). Protein metabolism is largely carried out in the distal colon which may contribute to significant increased chance of occurrence of distal colon cancer as compare to the development of proximal colon cancer. Metabolic activities in intestine are altered by protein rich diet with low carbohydrate levels leading to depletion of production of anticancerous metabolites such as plant-based phenol derivatives and increase in levels of hazardous metabolic products (Russell et al. 2011). Particularly, SCFAs play a key role in modulation of autophagy and are implicated in protective role in colon and liver cancers (Bindels et al. 2012; Donohoe et al. 2011; Hu et al. 2011). Anticancer and antioxidant properties of plant metabolites are attributed to phytochemicals such as phytophenols. Microbiota induced enzyme catalyzed reactions produce or catalyze polyphenols and can affect carcinogenesis (DeWeerdt 2011; Dutton and Turnbaugh 2012; Schwabe and Jobin 2013a; Van Duynhoven et al. 2011). Similarly, microbiota affects the activity of phytoestrogens such as lignans which have proven anticancer properties and therefore, modulates carcinogenesis (Chang and Keasling 2006; Dutton and Turnbaugh 2012; Mabrok et al. 2011). Although anticancer activities of phytochemicals are regulated by microbiota, characterization of microbial species and underlying molecular and cellular pathways is needed. Microbiota also plays a significant role in metabolism of xenobiotics (Haiser and Turnbaugh 2012). Intrinsically, it modulates the biological activities and side effects of anticancer agents. For instance, liver-inactivated irinotecan is reactivated by β-glucuronidase resulting in several side effects (Wallace et al. 2010). However, treatment

in combination with antibiotics or β-glucuronidase blockers inhibits these side effects.

Microbiota affects cancer development by metabolism of several carcinogens leading to their activation and inactivation; such as that of alcohol derivatives which are responsible for about 3.6% of cancers worldwide (Schwabe and Jobin 2013a; Seitz and Stickel 2007). Acetaldehyde is responsible for promoting alcohol genotoxicity and diseased conditions and is present at depleted levels in experimental germ-free mice models. Bacteria mediated production of acetaldehyde is vital in oral cancer due to its limited metabolism which significantly increases its concentration in the blood (Seitz and Stickel 2007). Implications of microbiota in metabolism of hormones have also been reported (Plottel and Blaser 2011). For instance, it modulates the development of oestrogen-mediated cancers by affecting its enterohepatic circulation and controlling its excreted levels (Plottel and Blaser 2011).

Microbiota mediated activation of TLRs and NLRs

TLRs-based recognition of patterns of microorganisms is a major inflammation promoting response of innate immunity (Moresco et al. 2011). Several studies show that bacterial MAMPS and TLRs mediate cancer development and progression. Toll-like receptor 4 (TLR4), which is responsible for recognition of lipopolysaccharides (LPS) present in Gram-negative bacterial cell wall induce cancer development as shown in experimental mice models with TLR4 depleted levels that had decreased tumor development as compared to the mice with constitutively expressed TLR4 and increased rate of carcinogenesis (Dapito et al. 2012; Fukata et al. 2007, 2010; Mittal et al. 2010; Ochi et al. 2012). Toll-like receptor 2 (TLR2) involved in recognition of peptidoglycans in bacterial cell wall mediates gastric carcinoma (Tye et al. 2012). TLRs induce cancer development through cells produced from bone marrow. A major procancer effect of TLR is activation of cellular survival signaling cascades, which are promoted by induction of nuclear factor-κβ (NF-κβ) (Tye et al. 2012). Besides strong evidences of expression of TLRs in cancer cells, studies are required to find out if the TLR signaling cascades directly affect cellular survival in carcinogenesis. Point mutations in myeloid differentiating primary response 88 (MYD88) in human lymphomas activate NF-κβ that indicates the prosurvival activity of MYD88. Microbiota-mediated activation of TLRs in intestine promotes carcinogenesis by stimulating IL17 and IL23 signaling cascades (Grivennikov et al. 2012). Interestingly, disruption of both IL17 and IL23 leads to inhibition of carcinogenesis (Grivennikov et al. 2012; Wu et al. 2009). TRL-induced tumor proliferation is modulated via a diverse group of mitogens released from stromal fibroblasts with TLR expression (Dapito et al. 2012; Fukata et al. 2007; Neufert et al. 2013). Signaling cascades utilized by various types of TLRs are multifunctional in nature and can affect malignant tumors and normal cells equally. For instance, MYD88 safeguards normal epithelia. In contrast, inhibition of MYD88 expression leads to cancer development in experimental models with significant levels of epithelial damage (Salcedo et al. 2010). It also promotes IL-18 signaling and its deficiency may induce carcinogenesis by disrupting IL-18-dependent signaling cascades (Schwabe and Jobin 2013a).

NLRs are a family of pattern recognition receptors (PRRs) with a key nucleotide-binding oligomerization domain (NOD) (Elinav et al. 2011). NOD2, a key NRL associated with Crohn's disease, has been linked with increased chances of CRC development in numerous cohorts when disrupted via polymorphisms (Cho 2008; Khor et al. 2011). Similarly, decreased expression levels of NOD2 induces CRC in experimental mice models (Couturier-Maillard et al. 2013). NOD2 also modulates immune responses to bacterial microbiota as indicated by higher susceptibility to infections in experimental mice models with NOD2 knocked out (Kobayashi et al. 2005). Intriguingly, intestinal dysbiosis has been detected in experimental mice models with NOD2 knocked out and patients with mutated NOD2 (Petnicki-Ocwieja et al. 2009).

NOD-like receptor family pyrin domain containing 6 (NLRP6) is also implicated in microbiota induced carcinogenesis and interaction of gut microbiota with host. It is part of inflammasomes and actively induces their activation as suggested by depleted IL18 levels in *Nlrp6*$^{-/-}$ mice models (Hu et al. 2013). The results correlate with the findings from studies conducted on *Nlrp2*$^{-/-}$ mice models as *Nlrp6*$^{-/-}$ mice models also have increased chances of development of CRC and colitis. Dysbiosis in gut microbiota of *Nlrp6*$^{-/-}$decreases immune system mediated inflammation and expression of IL8 ultimately leading to carcinogenesis (Hu et al. 2013). Similarly, decreased susceptibility to CRC in experimental mice models subjected to treatment with IL-6 receptor-based antibodies indicate that IL6 induces carcinogenic effects of *Nlrp6*$^{-/-}$and *Nlrp2*$^{-/-}$ (Hu et al. 2013). Similarly, NOD1 has been implicated in intestinal immune system and inflammatory bowel disease (McGovern et al. 2005). Decreased NOD1 levels are associated with deregulation of intestinal barrier and induction of CRC (Grivennikov et al. 2012). However, treatment with antibiotics leads to disruption of gut microbiota and suppression of CRC. Likewise, other NLRs such as NLRP3, NLRR, and NLRC4 also play a key role in development of colitis-induced carcinogenesis. However, limited data is available on their functional characterization and underlying mechanism of action.

Microbiota and cancer therapy

Microbiota modulates metabolic pathways of the host, immune responses, and inflammation; thereby playing a key role in cancer initiation and development. Several studies have validated that gut microbiota is involved in carcinogenesis both in epithelial cell lines and sterile environments (Dzutsev et al. 2015). Despite the significant advances in development of anticancer therapeutics, particularly immunotherapeutics, response to anticancer therapy is either very low or not observed in a large number of cancer patients. This may be explained in perspective of regulation of the response to cancer therapy and its target efficiency by gut microbiota. This section focuses on regulation of patient response chemotherapy, immunotherapy, and radiotherapy by host microbiome particularly gut microbiota.

Gut microbiota and chemotherapy

Cytotoxic therapeutics still remain the largest anticancer agents being developed and used for the treatment of cancer today (Roy and Trinchieri 2017). Majority of the cytotoxic anticancer therapeutics are alkylating substances, compounds targeting metabolic pathways, spindle poisons, cytotoxic antimicrobial agents, and heavy metals such as platinum. Whilst on the other hand, chemotherapy induces cellular DNA damage and targets cell division in growing tumors. Chemotherapy-induced targeting of cellular organelles such as mitochondria also lead to cytotoxicity (Sancho-Martínez et al. 2012). However, the major disadvantage of chemotherapy is its broad range specificity to cause toxicity in tissues with comparatively increased rate of cell division (Mitchell 2006).

Gut microbiota regulates response to cancer therapy via several mechanisms including immunomodulation, translocation, and enzymatic degradation. Translocation refers to the passage of commensal and pathogenic microbiota across epithelial barrier of gut to induce systemic effects that regulate the morbidity of chemotherapeutic agents (Samet et al. 2013). Though it was first described in 1960s, the relationship of translocation with modulation of efficiency and efficacy of anticancer therapy remains unclear. For instance, phosphamide cyclophosphamide (CTX) induces its anti-cancerous effects by interfering with numerous immunological signaling cascades (Kroemer et al. 2013; Schiavoni et al. 2010). Studies conducted by Viaud et al. on experimental mice models for investigation of the role of commensal microbiome of small intestine in response to CTX exposure indicated that CTX disrupts intestinal barrier and promotes translocation of commensal microbiota into adjacent lymphatic system (Viaud et al. 2013). While the total bacterial count in small intestine remained the same Decrease in population of *lactobacilli* and *enterococci* was noticed. Moreover, several bacterial species such as *Lactobacillus murinus* and *Lactobacillus johnsonii* were required for activation of CTX-induced immunological responses of type 17 T helper cells. Later on, another study by same group showed the necessity of *Enterococcus hirae* and *Barnesiella intestinihominis* in mediating antitumor effects of CTX in microbiota depleted experimental mice models. Exposure of experimental mice models to CpG oligodeoxynucleotides showed that microbiota stimulates cytokine production by myeloid cells whilst no similar activity was detected in microbiota depleted experimental mice models (Iida et al. 2013). Furthermore, antibiotic treatment in controls led to significant reduction in efficacy of chemotherapeutic-based eradication of cancer cells; whilst germ-free experimental models did not respond to the treatment.

Gut microbiota directly impacts the pharmacokinetics of anticancer drugs, their antitumor activity, and their cellular toxicity at several levels (Grootaert et al. 2011 #204). Metabolism and bioavailability of several drugs rely on their exposure to a variety of host and microbiota-produced enzymes prior to entering the bloodstream (Feng et al. 2015 #205). Nitroreduction of misonidazole and metabolism of methotrexate CPT-11 (topoisomerase I poison) has been demonstrated to be modulated by gut microbiota (Haiser and Turnbaugh 2013 #206).

Besides oral anticancer therapeutics, partial metabolism of injected drugs occurs in the liver where they are also exposed to the gut microbiota. Irinotecan—an anticancerous drug used for the treatment of CRC, is converted into SN-38 in liver and then into SN-38-G by UDP-glucuronosyltransferases produced by the host body. However, it can be metabolized by the β-glucuronidase produced by gut microbiota into SN-38 which subsequently can induce cellular toxicity in intestine.

Goubet et al. (2018) identified NOD2 as regulator of the efficacy of CTX treatment. Experimental mice models with mutated intestinal NOD2 showed comparatively better response to CTX. The study also revealed that population count of *B. intestinihominis* in proximal colon was increased after CTX exposure. Increased count of *B. intestinihominis* and elevated levels of antitumor activity of CTX in experimental mice models with NOD2 knocked out were present as cause and effect. Mice with mono-association to *B. intestinihominis* had abundant polyfunctional immune responses. In contrast, combination of *B. intestinihominis* with CTX against a vast range of cancer indicated promising results in mice with depleted microbiota after treatment with antibiotics. The regulation of response to anticancer therapy by gut microbiota has also been validated by Iida et al. (2013).

Tumor infiltrating hematopoietic cells lead to production of ROS during treatment with platinum derivative antitumor compounds. In experimental mice model with exposure to antibiotics, decreased levels of myeloid cell production was involved in disruption of effects of oxaliplatin-based anticancer therapy against lymphoma. Cellular toxicity in the gastrointestinal region is a common hallmark of toxicity induced by chemotherapy which results in mucositis ultimately leading to mortality (Widmer 2014 #202). Moreover, it causes dose-limitation which impacts the efficiency of anticancer therapy. CPT-11—a topoisomerase I targeting molecule increases presence of *Clostridium* cluster XI which is a pathogen (Alexander 2017 #203).

Findings from several studies have indicated that the interaction of anticancer chemotherapeutics with bacterial microbiome can affect their efficiency. For instance, activity of 10 out of 30 chemotherapeutics was suppressed in the presence of nonpathogenic bacterial species *E. coli* and *Listeria welshimeri* (Lehouritis et al. 2015) due to biotransformation as indicated via mass spectrometry analysis. However, the targeting efficiency of 6 drugs was increased. Intratumor inoculation of *E. coli* confirmed the suppression of anticancer activity of gemcitabine (Lehouritis et al. 2015). In case of doxorubicin, its efficacy remained unchanged in microbiota depleted experimental mice models. However, increased population of *Parabacteroides distasonis* disrupted its anticancer activity in experimental mice models treated with antimicrobials (Selwyn et al. 2015). Underlying mechanism of interference of microbiota with antitumor activity of chemotherapeutic agents remains unclear except for platinum derivatives and CTX (Viaud et al. 2013). In summary, these findings are suggestive of the modulation of chemotherapy by gut microbiota.

Gut microbiota and immunotherapy

Resistance to chemotherapy in large number of patients with increased incidences of reoccurrence of tumor development has been reported (Roy and Trinchieri 2017). Over the past few years, immunotherapy has shown promising results for the treatment of hematopoietic and solid carcinoma. For the very first time, long-lasting response to immunotherapy has been indicated in patients with resistance to all previously available anticancer therapeutic strategies (Yang 2015). Nevertheless, the susceptibility of cancer cells to immunotherapeutics and regulation by immune system has limited the efficiency of immunotherapy.

Treatment with anti-interleukin 10 (IL-10) and CpG oligonucleotides suppresses growth of colon cancer in experimental mice models (Goubet et al. 2018). Findings from previous studies indicate that tumor necrosis factor α (TNF-α) modulates necrotizing properties in these experimental mice model. Noticeably, treatment with antibiotics suppressed the activity of TNF-α and therapeutic efficiency of anti-IL10 administered along with CpG (Iida et al. 2013). Overpopulation of *Alistipes shahii* was detected in tumor samples isolated from colon of experimental mice models responding to immunotherapy and had a strong correlation with expression of TNF-α. The expression of TNF-α was increased when an oral administration of *A. shahii* was performed in contrast to the antibiotics-treated experimental mice models. Oral gavage of *A. shahii* promoted TNF-α expression by myeloid cells thereby indicating that it impacts myeloid cells-based immune responses to boost the response to immunotherapy (Goubet et al. 2018).

Similarly, implication of commensal microbiota of the gut in regulating the therapeutic efficiency of immunotherapeutics, particularly, those which are based on inhibition of immune checkpoints, has been reported. Ipilimumab, a cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) prolongs survival rate in metastatic melanoma (Robert et al. 2011) and relies on intestinal microbiota to revive T cell activity. Immunocheckpoint blockers as well as monoclonal antibodies targeting CTLA-4 and programmed cell death protein-1 (PD1) and it's ligand (PDL-1) are proven to show therapeutic efficiency in patients with lung cancer (Sharma and Allison 2015). Administration of *Bifidobacterium* sp. improved therapeutic efficiency of PD-L1 in experimental mice models with disrupted gut microbiota due to elevated levels of cancer-specific CD8+ cell activity (Sivan et al. 2015). These findings are supported by parallel studies involving the investigation of implications of gut microbiota in regulation of response to immune checkpoint blockers (Chaput et al. 2017; Frankel et al. 2017; Gopalakrishnan et al. 2018; Matson et al. 2018; Routy et al. 2017, 2018). Effects of antibiotics intake in response to immunotherapeutics were studied in a large cohort of patients with progressive carcinomas. Patients undergoing antibiotics treatment shortly or during administration of anti-PD-1 had lower survival rate in contrast with patients not intaking antibiotics. It suggests that the depletion of gut microbiota after treatment with antibiotics could therapeutically disrupt response to anticancer immunotherapeutics. Study conducted on lung and renal cancer patients by Routy et al. suggests that dysbiosis in gut microbiota can be induced via antibiotics leading to disrupted responses to anti-PD1 mAb-induced therapeutic efficacy (Goubet et al. 2018). Overpopulation of commensal bacterial species *Akkermansia muciniphila* was detected in stool samples of the patients with increased rate of development of infection. Similarly, a TH1 cell immune response against *A. muciniphila* present in blood and expression of Interferon gamma (IFNγ) by CD4+ cells were linked with improved clinical results during immunotherapy with anti-PD1. Results from another study correlate with these findings in patients with melanoma (Matson et al. 2018). Similarly, scaling of dysbiosis in stools samples collected

from patients with melanoma suggested the presence of resistance to PD-1-based immunotherapy comprising bifidobacteria and enterococci. Hundred percent response to the immunotherapeutics was present in patients harboring *A. muciniphila* compared with the expected response rate of 40%. To sum up, these studies suggest that gut microbiota significantly influences the response of patients and experimental mice models to cancer therapy.

Gut microbiota and radiotherapy

Ionizing radiation therapy (RTX) induces genotoxicity in cancer cells and has proven to show long-lasting curative results for localized carcinomas. Previously understood mechanisms of action of RTX was suggestive of production of ROS for targeting cellular DNA damage. However, non-target systemic effects including genomic instability and interference with the immune responses have also been reported (Mavragani et al. 2016). Several other systemic effects are induced by interruption of the gap-junction proteins involved in cellular communications and by the production of extracellular response stimulators such as ROS and exosomes (Al-Mayah et al. 2015; Pateras et al. 2015; Vacchelli et al. 2013).

The underlying mechanism of regulation of response to RTX by microbiota is unclear. Localized targeted RTX can promote immune system mediated cytotoxicity of cancer cells and systemic immune responses (Kroemer et al. 2013). Due to the fact that microbiota modulates the immunogenic cytotoxicity in conventionally available anticancer treatment strategies, similar role can also be suggested in perspective of RTX mediated immune responses (Iida et al. 2013). RTX significantly damages bone marrow and epithelia such as mucosal lining of the digestive tract. Disruption of the microbiota after RTX exposure in patients and experimental mice models have been proposed to induce diarrhea, colitis, and bone diseases (Broin et al. 2015; Kroemer et al. 2013; Touchefeu et al. 2014; Vanhoecke et al. 2016). RTX also promotes apoptotic cell death in intestine, disruption of the intestinal barrier, and interruption of microbiota (Barker et al. 2015). These alterations mediate immune responses in intestine resulting in gut inflammation and alterations in the microbiota-modulated systemic functions (Belkaid and Hand 2014; Broin et al. 2015).

RTX-promoted mucositis and body infections impact the completion of anticancer therapy. Intestinal toxicity induced by TRX is regulated by TLR3. Experimental TLR3$^{-/-}$ mice models are prone to p53-reliant RTX promoted apoptotic cell death, but are resistant to TLR3-dependent cell death induced after RTX-mediated RNA leakage (Takemura et al. 2014; Takemura and Uematsu 2017). Experimental TLR3$^{-/-}$ mice models have prolonged survival rate after treatment with RTX and have reduced intestinal cytotoxicity in contrast to the wild type mice, indicating that inhibition of TLR3 signaling cascade might minimize the intestinal toxicity caused by RTX (Takemura et al. 2014; Takemura and Uematsu 2017). RTX results in cytotoxicity and tissue damage by inducing double stranded breaks (DSBs) in DNA that activate melanoma type-2 inflammasome (Hu et al. 2016). On the other hand, a probiotic bacterial specie *Lactobacillus rhamnosus* GG activates TLR2 and protects intestine against RTX induced cellular damage by relocating the cyclooxygenase 2 (COX2) producing cells and generating ROS which activate nuclear factor erythroid 2-related factor-2 (NRF2) mediated cellular protection (Jones et al. 2015). Interestingly, several probiotics such as *Lactobacillus acidophilus, Bifidobacterium bifidum*, and certain *Streptococcus* spp. have shown promising results in clinical trials for suppressing the cytotoxic effects of RTX (Wardill et al. 2018). Similarly, intake of *Lactobacillus brevis* CD2 by head and neck cancer patients undergoing RTX reduced the incidence of RTX-induced mucositis (Hou et al. 2018).

Probiotic intake suppresses RTX-induced cellular damage. However, experimental germ-free mice models have higher survival rate than wild type mice after exposure to total body irradiation (TBI) (Cong and Zhang 2018). After RTX, experimental germ-free mice models possess less apoptotic endothelial cells in the intestine in contrast to the wild type mice (Cong and Zhang 2018). Development of resistance against TBI in experimental germ-free mice models might be due to depleted populations of pathogenic and commensal microbiota which is present in wild type mice and might cause intestinal inflammation immediately after RTX. One of the mechanisms responsible for resistance of experimental germ-free mice models to TBI is expression of angiopoietin-like 4 (ANGPTL4) blockade of lipase which is inhibited in wild type mice (Cong and Zhang 2018). ANGPTL4 affects metabolic pathways, tumor development, and tissue repair in a variety of ways (Carbone et al. 2018). Experimental germ-free ANGPTL4 knockout mice models are prone to intestinal cytotoxicity. In contrast, bacterial species that regulate production of ANGPTL4 are found to be involved in conferring protection against RTX-mediated colitis suggesting the presence of resistance in mice administered with probiotics and germ-free mice. In summary, microbiota regulates the intestinal damage induced by RTX. However, molecular and cellular underlying mechanisms of RTX's non-target effects and their modulation via microbiota are needed to be established which will be useful for development of novel therapeutic strategies with better efficacy.

Concluding remarks

The hypothesis that microbiota plays a key role in modulation of cancer development and response to cancer therapy is now supported by strong evidences. The therapeutic efficiency and efficacy of anticancer therapeutics is

largely dependent on gut microbiota. However, it impacts the response to anticancer therapy both in intestinal and extraintestinal tissues. Complex biological systems are a major barrier in the investigation of the molecular and cellular pathways regulated via host-microbiota interplay. However, systemic clinical studies are needed to be developed using interdisciplinary approaches which can provide better and novel insights into the underlying mechanisms of these pathways.

Meanwhile, gut microbiota can serve as a potential biomarker for carcinogenesis and response to cancer therapy, it can be evaluated by studying host dysbiosis via metagenomic, molecular biology, and metabolomics, and mass spectrometry-based approaches. This will also allow the development of probiotic-based treatment strategies for cancer patients for reduction of the off-target impacts of cancer therapy and promotion of the host immune system mediated anticancer activities. Additionally, microbiota can be exploited for the prolonging cancer survival rates and improvement of efficacy of conventionally available anticancer therapies. In this perspective, translational and clinical sciences may contribute significantly if the potential of human microbiome as a therapeutic target has to be established.

Funding Not applicable.

Compliance with ethical standards

Conflict of interest We declare that we have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

Abdulamir AS, Hafidh RR, Bakar FA (2010) Molecular detection, quantification, and isolation of *Streptococcus gallolyticus* bacteria colonizing colorectal tumors: inflammation-driven potential of carcinogenesis via IL-1, COX-2, and IL-8. Mol Cancer 9:249

Alam B, Saporoschetz I, Epstein S (1971) Synthesis of nitrosopiperidine from nitrate and piperidine in the gastro-intestinal tract of the rat. Nature 232:199

Allen-Vercoe E, Strauss J, Chadee K (2011) *Fusobacterium nucleatum*: an emerging gut pathogen? Gut Microbes 2:294–298

Al-Mayah A et al (2015) The non-targeted effects of radiation are perpetuated by exosomes. Mutat Res Fundam Mol Mech Mutagen 772:38–45

Apostolou P, Tsantsaridou A, Papasotiriou I, Toloudi M, Chatziioannou M, Giamouzis G (2011) Bacterial and fungal microflora in surgically removed lung cancer samples. J Cardiothorac Surg 6:137

Arthur JC et al (2012) Intestinal inflammation targets cancer-inducing activity of the microbiota. Science 338:120–123

Attene-Ramos MS, Wagner ED, Plewa MJ, Gaskins HR (2006) Evidence that hydrogen sulfide is a genotoxic agent. Mol Cancer Res 4:9–14

Baek MK et al (2010) Lithocholic acid upregulates uPAR and cell invasiveness via MAPK and AP-1 signaling in colon cancer cells. Cancer Lett 290:123–128

Barker HE, Paget JT, Khan AA, Harrington KJ (2015) The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat Rev Cancer 15:409

Bayerdörffer E et al (1995) Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. Lancet 345:1591–1594

Belcheva A et al (2014) Gut microbial metabolism drives transformation of MSH2-deficient colon epithelial cells. Cell 158:288–299

Belkaid Y, Hand TW (2014) Role of the microbiota in immunity and inflammation. Cell 157:121–141

Belkaid Y, Naik S (2013) Compartmentalized and systemic control of tissue immunity by commensals. Nat Immunol 14:646–653

Bernstein C, Holubec H, Bhattacharyya AK, Nguyen H, Payne CM, Zaitlin B, Bernstein H (2011) Carcinogenicity of deoxycholate, a secondary bile acid. Arch Toxicol 85:863–871

Bindels LB et al (2012) Gut microbiota-derived propionate reduces cancer cell proliferation in the liver. Br J Cancer 107:1337

Boleij A et al (2014) The Bacteroides fragilis toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clin Infect Dis 60:208–215

Bonnet M et al (2014) Colonization of the human gut by *E. coli* and colorectal cancer risk. Clin Cancer Res 20:859–867

Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas M-E (2016) Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med 8:42

Broin P et al (2015) Intestinal microbiota-derived metabolomic blood plasma markers for prior radiation injury. Int J Radiat Oncol Biol Phys 91:360–367

Carbone C et al (2018) Angiopoietin-like proteins in angiogenesis inflammation and cancer. Int J Mol Sci 19:431

Carbonero F, Benefiel AC, Alizadeh-Ghamsari AH, Gaskins HR (2012) Microbial pathways in colonic sulfur metabolism and links with health and disease. Front Physiol 3:448

Castellarin M et al (2012) *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma. Genome Res 22:299–306

Caygill CP, Hill MJ, Braddick M, Sharp JC (1994) Cancer mortality in chronic typhoid and paratyphoid carriers. Lancet 343:83–84

Chan PJ, Seraj IM, Kalugdan TH, King A (1996) Prevalence of mycoplasma conserved DNA in malignant ovarian cancer detected using sensitive PCR-ELISA. Gynecol Oncol 63:258–260

Chang MC, Keasling JD (2006) Production of isoprenoid pharmaceuticals by engineered microbes. Nat Chem Biol 2:674–681

Chanudet E et al (2007) Chlamydiae and Mycoplasma infections in pulmonary MALT lymphoma. Br J Cancer 97:949

Chaput N et al (2017) Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 28:1368–1379

Chen GY, Shaw MH, Redondo G, Núñez G (2008) The innate immune receptor Nod1 protects the intestine from inflammation-induced tumorigenesis. Cancer Res 68:10060–10067

Chen W, Liu F, Ling Z, Tong X, Xiang C (2012) Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. PLoS One 7:e39743

Cho JH (2008) The genetics and immunopathogenesis of inflammatory bowel disease. Nat Rev Immunol 8:458

Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG (2014) Minireview: Gut microbiota: the neglected endocrine organ. Mol Endocrinol 28:1221–1238

Cong J, Zhang X (2018) How human microbiome talks to health and disease. Eur J Clin Microbiol Infect Dis 37:1595–1601

Consortium HMP (2012) Structure, function and diversity of the healthy human microbiome. Nature 486:207–214

Cotillard A et al (2013) Dietary intervention impact on gut microbial gene richness. Nature 500:585
Couturier-Maillard A et al (2013) NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. J Clin Investig 123(2):700–711
Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède J-P (2010) *Escherichia coli* induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proc Natl Acad Sci 107:11537–11542
Dapito DH et al (2012) Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell 21:504–516
De Martel C, Plummer M, Parsonnet J, Van Doorn L, Franceschi S (2009) Helicobacter species in cancers of the gallbladder and extrahepatic biliary tract. Br J Cancer 100:194
Devkota S et al (2012) Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in Il10–/– mice. Nature 487:104
DeWeerdt S (2011) Food: the omnivore's labyrinth. Nature 471:S22–S24
Dong L, Li J, Liu Y, Yue W, Luo X (2012) Toll-like receptor 2 monoclonal antibody or/and Toll-like receptor 4 monoclonal antibody increase counts of Lactobacilli and Bifidobacteria in dextran sulfate sodium-induced colitis in mice. J Gastroenterol Hepatol 27:110–119
Donohoe DR, Garge N, Zhang X, Sun W, O'Connell TM, Bunger MK, Bultman SJ (2011) The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab 13:517–526
Dutton RJ, Turnbaugh PJ (2012) Taking a metagenomic view of human nutrition. Curr Opin Clin Nutr Metab Care 15:448–454
Dzutsev A, Goldszmid RS, Viaud S, Zitvogel L, Trinchieri G (2015) The role of the microbiota in inflammation, carcinogenesis, and cancer therapy. Eur J Immunol 45:17–31
Elinav E, Strowig T, Henao-Mejia J, Flavell RA (2011) Regulation of the antimicrobial response by NLR proteins. Immunity 34:665–679
Epplein M, Pawlita M, Michel A, Peek RM, Cai Q, Blot WJ (2013) Helicobacter pylori protein—specific antibodies and risk of colorectal cancer. Cancer Epidemiol Prev Biomark 22(11):1964–1974
Faith JJ et al (2013) The long-term stability of the human gut microbiota. Science 341:1237439
Feng R et al (2015) Transforming berberine into its intestine-absorbable form by the gut microbiota. Sci Rep 5:12155
Ferreri AJ et al (2012) *Chlamydophila psittaci* eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. J Clin Oncol 30:2988–2994
Fox JG, Wang TC (2007) Inflammation, atrophy, and gastric cancer. J Clin Investig 117:60–69
Fox JG et al (2004) Gastroenteritis in NF-κB-deficient mice is produced with wild-type *Camplyobacter jejuni* but not with *C. jejuni* lacking cytolethal distending toxin despite persistent colonization with both strains. Infect Immun 72:1116–1125
Frankel AE, Coughlin LA, Kim J, Froehlich TW, Xie Y, Frenkel EP, Koh AY (2017) Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia 19:848–855
Fukata M et al (2007) Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. Gastroenterology 133:1869–1869.e1814
Fukata M et al (2010) Constitutive activation of epithelial TLR4 augments inflammatory responses to mucosal injury and drives colitis-associated tumorigenesis. Inflamm Bowel Dis 17:1464–1473
Gagnière J et al (2016) Gut microbiota imbalance and colorectal cancer. World J Gastroenterol 22:501
Gamallat Y et al (2016) Lactobacillus rhamnosus induced epithelial cell apoptosis, ameliorates inflammation and prevents colon cancer development in an animal model. Biomed Pharmacother 83:536–541
Garaude J, Kent A, van Rooijen N, Blander JM (2012) Simultaneous targeting of toll-and nod-like receptors induces effective tumor-specific immune responses. Sci Transl Med 4:120ra116
Garrett WS (2015) Cancer the microbiota. Science 348:80–86
Garrett WS et al (2010) Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. Cell Host Microbe 8:292–300
Gill SR et al (2006) Metagenomic analysis of the human distal gut microbiome. Science 312:1355–1359
Gopalakrishnan V et al (2018) Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science 359:97–103
Goubet A-G, Daillère R, Routy B, Derosa L, Roberti PM, Zitvogel L (2018) The impact of the intestinal microbiota in therapeutic responses against cancer. Comptes rendus biologies 341(5):284–289
Grivennikov SI et al (2012) Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 491:254
Grootaert C et al (2011) Bacterial monocultures, propionate, butyrate and H_2O_2 modulate the expression, secretion and structure of the fasting-induced adipose factor in gut epithelial cell lines. Environ microbiol 13:1778–1789
Ha Y-H, Park D-G (2010) Effects of DCA on cell cycle proteins in colonocytes. J Korean Soc Coloproctol 26:254–259
Haiser HJ, Turnbaugh PJ (2012) Is it time for a metagenomic basis of therapeutics? Science 336:1253–1255
Haiser HJ, Turnbaugh PJ (2013) Developing a metagenomic view of xenobiotic metabolism. Pharmacol Res 69:21–31
Hajishengallis G, Darveau RP, Curtis MA (2012) The keystone-pathogen hypothesis. Nat Rev Microbiol 10:717
Han YW et al (2005) Identification and characterization of a novel adhesin unique to oral fusobacteria. J Bacteriol 187:5330–5340
Hold GL, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhya I (2014) Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? World J Gastroenterol WJG 20:1192
Holmes E, Li JV, Marchesi JR, Nicholson JK (2012) Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab 16:559–564
Hooper SJ, Crean S-J, Fardy MJ, Lewis MA, Spratt DA, Wade WG, Wilson MJ (2007) A molecular analysis of the bacteria present within oral squamous cell carcinoma. J Med Microbiol 56:1651–1659
Hou J, Zheng H, Li P, Liu H, Zhou H, Yang X (2018) Distinct shifts in the oral microbiota are associated with the progression and aggravation of mucositis during radiotherapy. Radiother Oncol 129(1):44–51
Hu S, Dong TS, Dalal SR, Wu F, Bissonnette M, Kwon JH, Chang EB (2011) The microbe-derived short chain fatty acid butyrate targets miRNA-dependent p21 gene expression in human colon cancer. PLoS One 6:e16221
Hu B et al (2013) Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. Proc Natl Acad Sci 110:9862–9867
Hu B et al (2016) The DNA-sensing AIM2 inflammasome controls radiation-induced cell death tissue injury. Science 354:765–768
Huttenhower C et al (2012) Structure, function and diversity of the healthy human microbiome. Nature 486:207
Huycke MM, Gaskins HR (2004) Commensal bacteria, redox stress, and colorectal cancer: mechanisms and models. Exp Biol Med 229:586–597

Iida N et al (2013) Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 342:967–970

Islami F, Kamangar F (2008) *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. Cancer Prev Res 1:329–338

Jones RM et al (2015) Lactobacilli modulate epithelial cytoprotection through the Nrf2 pathway. Cell Rep 12:1217–1225

Khor B, Gardet A, Xavier RJ (2011) Genetics and pathogenesis of inflammatory bowel disease. Nature 474:307

Klimesova K et al (2013) Altered gut microbiota promotes colitis-associated cancer in IL-1 receptor-associated kinase M deficient mice. Inflamm Bowel Dis 19:1266

Kobayashi KS, Chamaillard M, Ogura Y, Henegariu O, Inohara N, Nunez G, Flavell RA (2005) Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. Science 307:731–734

Kostic AD et al (2012) Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 22:292–298

Kostic AD et al (2013) *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 14:207–215

Kroemer G, Galluzzi L, Kepp O, Zitvogel L (2013) Immunogenic cell death in cancer therapy. Annu Rev Immunol 31:51–72

Le Chatelier E et al (2013) Richness of human gut microbiome correlates with metabolic markers. Nature 500:541

Lecuit M et al (2004) Immunoproliferative small intestinal disease associated with *Campylobacter jejuni* New England. J Med 350:239–248

Lehouritis P et al (2015) Local bacteria affect the efficacy of chemotherapeutic drugs. Sci Rep 5:14554

Lofgren JL et al (2011) Lack of commensal flora in *Helicobacter pylori*-infected INS-GAS mice reduces gastritis and delays intraepithelial neoplasia. Gastroenterology 140:210–220.e214

Louis P, Hold GL, Flint HJ (2014a) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12:661–672

Louis P, Hold GL, Flint HJ (2014b) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12:661

Lupp C, Robertson ML, Wickham ME, Sekirov I, Champion OL, Gaynor EC, Finlay BB (2007) Host-mediated inflammation disrupts the intestinal microbiota and promotes the overgrowth of Enterobacteriaceae. Cell Host Microbe 2:119–129

Mabrok HB, Klopfleisch R, Ghanem KZ, Clavel T, Blaut M, Loh G (2011) Lignan transformation by gut bacteria lowers tumor burden in a gnotobiotic rat model of breast cancer. Carcinogenesis 33:203–208

Matson V et al (2018) The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359:104–108

Mavragani IV, Laskaratou DA, Frey B, Candéias SM, Gaipl US, Lumniczky K, Georgakilas AG (2016) Key mechanisms involved in ionizing radiation-induced systemic effects. A current review. Toxicol Res 5:12–33

McGovern DP et al (2005) Association between a complex insertion/deletion polymorphism in NOD1 (CARD4) and susceptibility to inflammatory bowel disease. Hum Mol Genet 14:1245–1250

Mima K et al (2015) Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. Gut 341(5):284–289

Minemura M, Shimizu Y (2015) Gut microbiota and liver diseases. World J Gastroenterol WJG 21:1691

Mitchell EP (2006) Gastrointestinal toxicity of chemotherapeutic agents. Semin Oncol 33(1):106–120

Mittal D, Saccheri F, Vénéreau E, Pusterla T, Bianchi ME, Rescigno M (2010) TLR4-mediated skin carcinogenesis is dependent on immune and radioresistant cells. EMBO J 29:2242–2252

Moresco EMY, LaVine D, Beutler B (2011) Toll-like receptors. Curr Biol 21:R488–R493

Morgan XC et al (2012) Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. Genome Biol 13:R79

Nath G, Singh H, Shukla V (1997) Chronic typhoid carriage and carcinoma of the gallbladder. Eur J Cancer Prev 6:557–559

Nešić D, Hsu Y, Stebbins CE (2004) Assembly and function of a bacterial genotoxin. Nature 429:429

Neufert C et al (2013) Tumor fibroblast-derived epiregulin promotes growth of colitis-associated neoplasms through ERK. J Clin Investig 123:1428–1443

Nougayrède J-P et al (2006) *Escherichia coli* induces DNA double-strand breaks in eukaryotic cells. Science 313:848–851

Nyangale EP, Mottram DS, Gibson GR (2012) Gut microbial activity, implications for health and disease: the potential role of metabolite analysis. J Proteome Res 11:5573–5585

Ochi A et al (2012) MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. J Exp Med 209:1671–1687

Ohnishi N et al (2008) Transgenic expression of *Helicobacter pylori* CagA induces gastrointestinal and hematopoietic neoplasms in mouse. Proc Natl Acad Sci 105:1003–1008

Pateras IS et al (2015) The DNA damage response and immune signaling alliance: is it good or bad? Nature decides when where. Pharmacol Ther 154:36–56

Patwa LG, Fan TJ, Tchaptchet S, Liu Y, Lussier YA, Sartor RB, Hansen JJ (2011) Chronic intestinal inflammation induces stress-response genes in commensal. *Escherichia coli*. Gastroenterology 141:1842–1851.e1810

Perez-Chanona E, Trinchieri G (2016) The role of microbiota in cancer therapy. Curr Opin Immunol 39:75–81

Petnicki-Ocwieja T, Hrncir T, Liu Y-J, Biswas A, Hudcovic T, Tlaskalova-Hogenova H, Kobayashi KS (2009) Nod2 is required for the regulation of commensal microbiota in the intestine. Proc Natl Acad Sci 106:15813–15818

Philipp B (2011) Bacterial degradation of bile salts. Appl Microbiol Biotechnol 89:903–915

Plottel CS, Blaser MJ (2011) Microbiome malignancy. Cell Host Microbe 10:324–335

Pradere J-P, Dapito DH, Schwabe RF (2014) The Yin and Yang of toll-like receptors in cancer. Oncogene 33:3485–3495

Putze J et al (2009) Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae. Infect Immun 77:4696–4703

Quante M et al (2012) Bile acid and inflammation activate gastric cardia stem cells in a mouse model of Barrett-like metaplasia. Cancer Cell 21:36–51

Quigley EM (2013) Gut bacteria in health and disease. Gastroenterol Hepatol 9:560

Raza MH, Siraj S, Arshad A, Waheed U, Aldakheel F, Alduraywish S, Arshad M (2017) ROS-modulated therapeutic approaches in cancer treatment. J Cancer Res Clin Oncol 143:1789–1809

Robert C et al (2011) Ipilimumab plus dacarbazine for previously untreated metastatic melanoma New England. J Med 364:2517–2526

Routy B et al (2017) The influence of gut-decontamination prophylactic antibiotics on acute graft-versus-host disease and survival following allogeneic hematopoietic stem cell transplantation. OncoImmunology 6:e1258506

Routy B et al (2018) Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359:91–97

Roy S, Trinchieri G (2017) Microbiota: a key orchestrator of cancer therapy. Nat Rev Cancer 17(5):271–285

Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW (2013) Fusobacterium nucleatum promotes colorectal carcinogenesis by

modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe 14:195–206
Russell WR et al (2011) High-protein, reduced-carbohydrate weight-loss diets promote metabolite profiles likely to be detrimental to colonic health. Am J Clin Nutr 93:1062–1072
Salcedo R et al (2010) MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. J Exp Med 207(8):1625–1636
Samet A, Śledzińska A, Krawczyk B, Hellmann A, Nowicki S, Kur J, Nowicki B (2013) Leukemia and risk of recurrent *Escherichia coli* bacteremia: genotyping implicates *E. coli* translocation from the colon to the bloodstream. Eur J Clin Microbiol Infect Dis 32:1393–1400
Sanapareddy N et al (2012) Increased rectal microbial richness is associated with the presence of colorectal adenomas in humans. ISME J 6:1858
Sancho-Martínez SM, Prieto-García L, Prieto M, López-Novoa JM, López-Hernández FJ (2012) Subcellular targets of cisplatin cytotoxicity: an integrated view. Pharmacol Ther 136:35–55
Sartor RB, Mazmanian SK (2012) Intestinal microbes in inflammatory bowel diseases. Am J Gastroenterol Suppl 1:15–21
Schiavoni G et al (2010) Cyclophosphamide synergizes with type I interferons through systemic dendritic cell reactivation and induction of immunogenic tumor apoptosis. Cancer Res **(canres.2788.2010)**
Schwabe RF, Jobin C (2013a) The microbiome and cancer. Nat Rev Cancer 13:800–812
Sears CL, Myers LL, Lazenby A, Van Tassell RL (1995) Enterotoxigenic *Bacteroides fragilis*. Clin Infect Dis 20:S142–S148
Seitz HK, Stickel F (2007) Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer 7:599
Selwyn FP, Cui JY, Klaassen CD (2015) RNA-Seq quantification of hepatic drug processing genes in germ-free mice. Drug Metab Dispos 43:1572–1580
Senff NJ et al (2008) European organization for research and treatment of cancer and international society for Cutaneous Lymphoma consensus recommendations for the management of cutaneous B-cell lymphomas. Blood 112:1600–1609
Shanmughapriya S, Senthilkumar G, Vinodhini K, Das B, Vasanthi N, Natarajaseenivasan K (2012) Viral and bacterial aetiologies of epithelial ovarian cancer. Eur J Clin Microbiol Infect Dis 31:2311–2317
Sharma P, Allison JP (2015) The future of immune checkpoint therapy. Science 348:56–61
Shen S, Wong CH (2016) Bugging inflammation: role of the gut microbiota. Clin Transl Immunol 5:e72
Shen Z et al (2009) Cytolethal distending toxin promotes *Helicobacter cinaedi*-associated typhlocolitis in interleukin-10-deficient mice. Infect Immun 77:2508–2516
Sivan A et al (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350(6264):1084–1089
Smith JL, Bayles DO (2006) The contribution of cytolethal distending toxin to bacterial pathogenesis. Crit Rev Microbiol 32:227–248
Sobhani I et al (2011) Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 6:e16393
Stecher B et al (2012) Gut inflammation can boost horizontal gene transfer between pathogenic and commensal Enterobacteriaceae. Proc Natl Acad Sci 109:1269–1274
Taieb F, Petit C, Nougayrède J-P, Oswald E (2016) The enterobacterial genotoxins: cytolethal distending toxin and colibactin. EcoSal Plus. https://doi.org/10.1128/ecosalplus.ESP-0008-2016
Takemura N, Uematsu S (2017) Blockade of Tlr3 protects mice from lethal radiation-induced gastrointestinal syndrome: Tu-p6-9. Cytokine 100:152
Takemura N et al (2014) Blockade of TLR3 protects mice from lethal radiation-induced gastrointestinal syndrome. Nat Commun 5:3492
Touchefeu Y et al (2014) Systematic review: the role of the gut microbiota in chemotherapy-or radiation-induced gastrointestinal mucositis—current evidence and potential clinical applications. Aliment Pharmacol Ther 40:409–421
Travaglione S, Fabbri A, Fiorentini C (2008) The Rho-activating CNF1 toxin from pathogenic *E. coli*: a risk factor for human cancer development? Infect Agents Cancer 3:4
Tye H et al (2012) STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. Cancer Cell 22:466–478
Vacchelli E et al (2013) Trial watch: anticancer radioimmunotherapy. Oncoimmunology 2:e25595
Van Duynhoven J et al (2011) Metabolic fate of polyphenols in the human superorganism. Proc Natl Acad Sci 108:4531–4538
Vanhoecke BW, De Ryck TR, De Boel K, Wiles S, Boterberg T, Van de Wiele T, Swift S (2016) Low-dose irradiation affects the functional behavior of oral microbiota in the context of mucositis. Exp Biol Med 241:60–70
Viaud S et al (2013) The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. Science 342:971–976
Vijay-Kumar M et al (2010) Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science 328:228–231
Wallace BD et al (2010) Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science 330:831–835
Wang X, Huycke MM (2007) Extracellular superoxide production by *Enterococcus faecalis* promotes chromosomal instability in mammalian cells. Gastroenterology 132:551–561
Wang Y, Kasper LH (2014) The role of microbiome in central nervous system disorders. Brain Behav Immun 38:1–12
Wang T et al (2012a) Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. ISME J 6:320
Wang X, Yang Y, Moore DR, Nimmo SL, Lightfoot SA, Huycke MM (2012b) 4-Hydroxy-2-nonenal mediates genotoxicity and bystander effects caused by *Enterococcus faecalis*-infected macrophages. Gastroenterology 142:543–551.e547
Wardill HR, Van Sebille YZ, Ciorba MA, Bowen JM (2018) Prophylactic probiotics for cancer therapy-induced diarrhoea: a meta-analysis. Curr Opin Support Palliat Care 12:187–197
Windey K, De Preter V, Verbeke K (2012) Relevance of protein fermentation to gut health. Mol Nutr Food Res 56:184–196
Winter SE et al (2013) Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. Science 339:708–711
Wu S et al (2009) A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med 15:1016
Yang Y (2015) Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Investig 125:3335–3337
Yoshimoto S et al (2013a) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499:97
Yoshimoto S et al (2013b) Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature 499:97–101
Yu LX et al (2010) Endotoxin accumulation prevents carcinogen-induced apoptosis and promotes liver tumorigenesis in rodents. Hepatology 52:1322–1333
Zhan Y et al (2013) Gut microbiota protects against gastrointestinal tumorigenesis caused by epithelial injury. Cancer Res 73:7199–7210
Zhang H-L et al (2012) Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. J Hepatol 57:803–812
Zitvogel L, Galluzzi L, Viaud S, Vétizou M, Daillère R, Merad M, Kroemer G (2015) Cancer and the gut microbiota: an unexpected link. Sci Transl Med 7:271ps271