REVIEW ARTICLE

Microbiota and cancer: current understanding and mechanistic implications

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Abstract

During last few decades, role of microbiota and its importance in several diseases has been a hot topic for research. The microbiota is considered as an accessory organ for maintaining normal physiology of an individual. These microbiota organisms which normally colonize several epithelial surfaces are known to secrete several small molecules leading to local and systemic effects on normal biological processes. The role of microbiota is also established in carcinogenesis as per several recent findings. The effects of microbiota on cancer is not only limited to their contribution in oncogenesis, but the overall susceptibility for oncogenesis and its subsequent progression, development of coinfections, and response to anticancer therapy is also found to be affected by microbiota. The information about microbiota and subsequent contributions of microbes in anticancer response motivated researchers in development of microbes-based anticancer therapeutics. We provided current status of microbiota contribution in oncogenesis with special reference to their mechanistic implications in different aspects of oncogenesis. In addition, the mechanistic implications of bacteria in anticancer therapy are also discussed. We conclude that several mechanisms of microbiota-mediated regulation of oncogenesis is known, but approaches must be focused on understanding contribution of microbiota as a community rather than single organisms-mediated effects.

Keywords Carcinogenesis · Microbiome · Pharmacomicrobiomics · Anticancer · Infection

Introduction

Recently a large number of studies are accumulating linking role of microbiota with normal host physiology and subsequent disease progression. The disruption of normal microbiota, known as microbiota dysbiosis contributes to development of several clinical conditions related to physical to behavioral aspects [1, 2]. Plethora of literature is supporting the role of microbiota in several physical abnormalities including, gastrointestinal, neurological to cardiovascular, etc. [3, 4]. Moreover, studies are linking role of microbiota

with cancer and supporting its contribution in almost all aspect of carcinogenesis ranging from cancer susceptibility and progression to response for anticancer therapy [5, 6]. Literature is suggesting that correction of microbiota dysbiosis through beneficial probiotic bacteria can be beneficial in a large number of cancer types [7, 8]. In addition, several microbes have been found with anticancer potential and are being developed for effective anticancer therapy [9].

Though, several complexities are creating bottlenecks in integrating such therapeutic modalities in routine anticancer management practices, multiple strategies are devised to utilize information obtained from microbiota-related experiments for management of cancer. These complexities including, geographical and inter individual variability of microbiota, identification of key microbiota component affecting carcinogenic process, and identification of proper mechanistic information leading to microbiota-mediated oncogenic transformation. Herein, we draw attention to the mechanistic implications of microbiota in influencing different aspects of oncogenesis and its subsequent influence on development of anticancer management strategies.

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Microbiota and oncogenesis

The role of microbiota in oncogenesis is widely recognized in a number of studies. It is estimated that more than 20% of cancer cases are associated with infectious agents [10]. Several microorganisms are specifically linked with development of cancer, like *H, pylori* which is declared as a class I carcinogen by the World Health Organization and involved in gastric adenocarcinoma and mucosa associated lymphoid tissue (MALT) lymphoma [11]. *Chlamydia trachomatis, Escherichia coli, Salmonella enterica* are also suspiciously involved in cervical, colorectal, and gallbladder cancer, respectively [12–17]. In addition, microbiota dysbiosis involving modulation of several microbiota organisms is also linked with carcinogenesis [18]. The antibiotics-mediated microbial dysbiosis is also known to play important role in tumorigenesis in some recent studies [19]. Several mechanisms of microbiota dysbiosis-mediated tumorigenesis are also proposed recently (Fig. 1), though the collective information about contribution of each microbiota components and their subsequent involvement in carcinogenesis is still lacking. Several studies are available indicating causal role of microbiota dysbiosis and cancer. For example, the microbiota of cancer-associated area is found to be different from microbiota occupying nearby healthy mucosa [20, 21]. Several articles are available on types of microbiota components modulation in different cancer, but their specific links with carcinogenesis needs more attention to understand their mechanistic implications. Following section indicates some mechanisms possibly involved in microbiota-mediated cancer etiology. Table 1 also lists some specific microbial components and their mechanistic involvement in carcinogenesis.

Metabolic influence

The gut microbiota is primarily involved in providing energy from non-digested food substances and therefore the dietary components are a major factor deciding microbiota composition. Under certain situations, these microbiota-mediated metabolic products have ability to influence carcinogenicity and these effects range from activation and synthesis of carcinogen, to removal of carcinogen [22]. Several bacterial enzymes are involved in cancer and indicate towards involvement of microbiota in carcinogenesis. Figure 1B
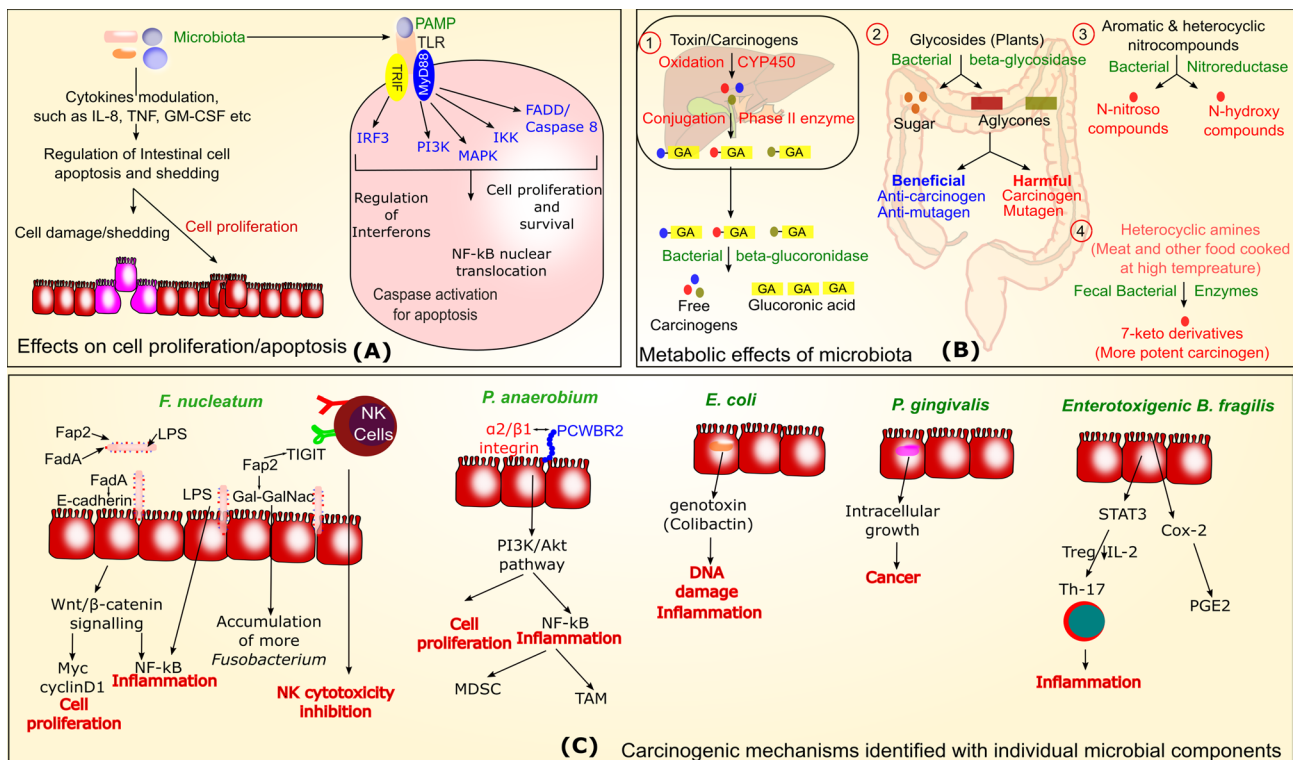

Fig. 1 Role of microbiota and individual microbiota components in carcinogenesis. The figure is divided in three sections and cancer-associated mechanisms are generally shown with red color while microbial components are shown with green color. Section **A** indicates influence of microbiota on cell growth or apoptosis related process, while section **B** and **C** indicate towards metabolic influence of microbiota and mechanisms associated with individual microbes on carcinogenesis, respectively

Table 1 The mechanistic implication of microbes in carcinogenesis

Sr. no	Bacteria	Cancer	Suggested key mechanisms	References
1	*Chlamydophila psittaci*	Ocular adenxal MALT lymphoma	Clonal selection of MALT for lymphoma development, chromosomal aberration caused by either genetic instability or oxidative DNA damage, affecting NF-kB pathway leading to anti-apoptotic effects Additional risk factor including autoimmune diseases	[84, 85]
2	*Porphyromonas gingivalis*	Oral cancer	Receptor upregulation on OSCC cells, EMT transition of normal oral epithelial cells, activation of IL-8 and MMP-9, inhibition of apoptosis and acceleration of cell cycle, conversion of ethanol to carcinogenic acetaldehyde	[86]
3	*Helicobacter pylori*	Gastric cancer	Inflammation induction through epithelial cell death and consequent repair of remaining cells leading to increase cell survival and proliferation and resultant precancerous lesions. Direct effects through bacterial effectors, such as cagA, vacA, and omp activating cell signaling pathways including PI3K/Akt, Ras, Raf, ERK, JAK/STAT, etc., leading to uncontrolled cell proliferation	[87, 88]
4	*Mycobacterium tuberculosis*	Lung cancer	DNA damage, production of epidermal growth factor (epiregulin). PD-1/PD-L1 pathway modulating T cell immune response mediating tumor metastasis	[78, 89]
5	*Chlamydia (Chlamydophila) pneumoniae*	Lung cancer	Inflammation mediated cell and DNA damage and consequent repair of cell injury contributes to increased cell proliferation and cancer. Superoxide radicals, TNF, IL-8, and IL1β secreted by monocytes in response to infection also contributes to cell and DNA damage and resultant carcinogenesis	[90]
6	*Salmonella typhi*	Gallbladder cancer	Chronic inflammation, typhoid toxin causes DNA damage and cell cycle alterations	[79]
7	*Streptococcus bovis*	Colon cancer	Inflammatory cytokines (such as IL1β, IL-8, TNF-alpha, and IL-6) may lead to formation of free radicals causing DNA alterations and cancer. Bacteria also degrade anticancer substances, such as tannic acid present in diet and contribute to cancer	[91, 92]
8	*Campylobacter jejuni*	Intestinal lymphoma	The CDT of bacteria cause dsDNA breaks in germinal centre B cells. Mutational events involving Pax5 and other oncogenes can lead to neoplastic changes	[93]
9	*Fusobacterium nucleatum*	Colorectal cancer	Induction of cell proliferation through Wnt/β-catenin signaling. Inflammation regulation and inhibition of natural killer cell cytotoxicity	[94]
10	*Bacteroides fragilis*	Colon cancer	BFT (*B. fragilis* toxin) cleaves cell surface protein E-cadherin and its cytoplasmic domain associate with β-catenin. The loss of E cadherin stimulate β-catenin signaling, induce c-myc and IL-8. Cause oxidative DNA damage, epithelial barrier damage, STAT3/TH17 immune response	[95]
11	*Citrobacter rodentium*	Colorectal cancer	Colonic crypt hyperplasia is regulated through Wnt/β-catenin, PI3K, and Notch pathway. MEK/ERK/NF-kB regulates inflammation. Other related mutagenic effects contribute to neoplasia	[96]
12	*Escherichia coli*	Colorectal cancer	Production of genotoxin leading to DNA damage and cell cycle modulation. Chronic inflammation and possibility to affect DNA repair	[13]
13	*Chlamydia trachomatis*	Cervical cancer	Acts as a cofactor with HPV for cancer development. Induces cell proliferation and inhibition of apoptosis	[12, 97]

*EMT-epithelial to mesenchymal transition, *IL-8* Interleukin8, *MMP9* Mettaloproteinase 9, *CDT* Cytolethal Distending Toxin, *OSCC* oral squamous cell carcinoma,

represents microbiota enzymes and their metabolic influence on carcinogenesis. It is found that prebiotics are known to increase beneficial *Bifidobacteria* and suppress these carcinogen metabolizing enzymes activities [23]. The probiotics are beneficial bacteria known for their ability to provide several anticancer effects and a number of articles are available for anticancer effects of probiotics [7, 8]. Therefore increasing the number of beneficial bacteria through fecal microbiota transplant is a well-known strategy for management of several gastrointestinal ailments [24]. The role of metabolic influence of microbiota is also evident through strong influence of dietary pattern on carcinogenesis. The excess energy intake in comparison to normal requirement is suggested to be linked with human cancer [25] and microbiota plays important role in this process through regulation of metabolic process [26].

Influence on cell growth

Development of cancer is directly linked with abnormal cell proliferation and it can be ranged from increased cellular proliferation to inhibition of cell death. The microbiota is known to regulate cell proliferation and regeneration under various conditions [27]. It has been found a long time ago that addition of dietary fiber in rat increases intestinal cell proliferation [28]. In addition, restriction of intestinal nutrients is known to induce intestinal atrophy even after providing nutrients through parenteral route [29]. The role of microbiota in digestion of dietary fiber and production of necessary metabolites indicate towards their involvement in regulating cell proliferation through this mechanism. It is known that certain bacterial fermentative metabolites, such as short chain fatty acid (SCFA) produced from nutrients are having ability to regulate cell proliferation [30, 31]. Several bacteria are known to produce certain proteins known as nucleomodulins with the ability to alter normal nuclear function and thereby influence cell growth. These nucleomodulins are also identified in bacteria suspiciously associated with cancer, thereby indicate towards potential involvement of these proteins in carcinogenesis [32]. In contrast, microbiota also has ability to both promote and inhibit cell death through regulating apoptosis and therefore contributing in intestinal mucosal epithelial cell inflammation and integrity [33]. It has been identified that germ free newborn mice has reduced interleukin 1β, tumor necrosis factor (TNF) and altered cell death [34]. Though this study was designed to evaluate effect of microbiota on brain development, but their results demonstrating microbiota-mediated regulation of major apoptotic regulator TNF demonstrate its ability to regulate cell death. Supporting this notion, probiotics bacteria *Lactobacillus rhamnosus* GG is able to inhibit cytokine-mediated apoptosis through activation of anti-apoptotic Akt/protein kinase B and inhibition of pro-apoptotic TNF, p38/MAPK, IL-1α or IFN-γ [35]. *L. rhamnosus* GG is also known to produce two proteins (p75 and p40) which activate Akt and promote colon epithelial cell growth and reduce TNF-mediated epithelial cell damage [36].

The pathogen associated molecular patterns (PAMP) of microbiota components are recognized through Toll like receptor (TLR) present on enterocytes and other surfaces to mount immunologic response. The toll-like receptor are known to show modulated expression during carcinogenesis and this is also considered to contribute in infectious complications among cancer patients [37]. The vice versa modulated TLR expression in response to different microbiota composition can also regulate cellular proliferation and death in multiple ways. The central TLR signaling pathways involving MAPK and PI3K play important role in regulating cell proliferation through TLR [38]. Figure 1A indicates different mechanisms through which microbiota can regulate cell proliferation and apoptosis.

Cancer therapy-associated microbiota modulation and complications

Anticancer therapy used to manage cancer also creates several effects on host microbiota and therefore generate several associated complications. These effects are mediated through multiple mechanisms, including dietary alterations, necessary surgical interventions and use of antibiotics for preventing post-surgical and other infections in addition to effects caused by anticancer drugs [39]. Therefore the reverse effect of microbiota modulation on anticancer therapy is also gaining importance and studies are conducted to understand and utilize this attribute for improving anticancer therapy treatment outcomes. The recent concept of pharmacomicrobiomics is considering effects of microbiota in drug response including anticancer therapy [40]. A common antimetabolite methotraxate is used in a number of clinical diseases including cancers, it has been found to inhibit several representative gut bacteria and alter microbiota composition [41]. An in vivo study on gut microbiota of colorectal cancer mouse model showed that anticancer drug 5-Fluorouracil (5-FU) can change microbiota diversity and composition. In addition, antibiotics-mediated gut microbiota disruption also contributed to reduced antitumor efficacy of 5-FU [42]. An important anticancer drug cyclophosphamide is also known to alter composition of microbiota in intestine and promote certain gram positive bacterial translocation to secondary lymphoid organs, where these bacteria stimulate production of pathogenic Th17 cells Th1 response [43]. Several other anticancer drugs are known to cause diarrhea through multiple mechanisms including killing of beneficial bacteria helping in digestion [44]. In contrast, microbiota components are also known to alter the response toward chemotherapeutic drugs and have been reviewed extensively. Microbiota components are able to modulate anticancer therapy outcomes through multiple mechanisms including resistance to anticancer drugs and immune check points inhibitors, modulation of metabolism, etc. Therefore it is suggested that these microbiota organisms can also serve as a prognostic and diagnostic marker for cancer [45]. Several microbial components itself possess anticancer activity and it is mediated by multiple mechanisms. Some microbes are known for production of anticancer substances [46], activation of antitumor immune response, and modulation of signaling pathways, etc. [6, 47]. Few bacteria known to possess anticancer activity are mentioned in Table 2 with their mechanistic implications.

Table 2 Mechanistic implications of bacteria in prevention of cancer

Sr. no	Bacteria	Suggested key anticancer mechanism	References
1	*Listeria monocytogenes*	The intracellular growth without extracellular cell to cell spread makes it an ideal vector for anticancer therapy. Acts as an immunomodulator to enhance anticancer T cell immune response	[98, 99]
2	*Bifidobacterium spp.*	Biotrasformation and production of antitumor metabolites from nutrition and drugs, competitive advantage in cancer microenvironment by exclusion of harmful microbiota and pathogens, modulation of cancer-associated cytokines and genes	[100]
3	*Salmonella typhimurium*	Attenuated bacterium is suggested as a delivery vehicle for anticancer therapy due to selective tumor targeting and anticancer response	[101]
4	*Streptococcus pyogenes*	Direct tumor cell lysis and activation of immune response by bacterial components leads to cancer cell death	[102]
5	*Clostridium novyi*	Activation of host antitumor immune response and direct destruction of tumor cell. Works on hypoxic area (which is generally difficult to treat with conventional radio and chemotherapy) due to anaerobic nature of bacteria	[103, 104]
6	*Bacillus calmette Guerin*	Used as immunotherapy for prevention of cancer relapse and progression. Elevate the level of IL-2 and mediate anticancer activity by type 1 immune response	[105]
7	*Serratia marcescens*	Produce several metabolites such as, extracellular metalloproteinase serralysin, and prodigiosin with anticancer potential	[106, 107]
8	*Corynebacterium diptheriae*	Diptheria exotoxin possess antitumor activity and used as a immunotoxins consisting toxin with additional targeting element	[108]

Microbiota, inflammation and cancer-associated signaling pathways

In addition to above mentioned mechanisms, microbiota is also known to alter several important signaling pathways leading to progression or inhibition of cancer. Some of these signaling pathways are already discussed in earlier section, but some other bacteria-specific signaling events leading to carcinogenesis are mentioned in Fig. 1C. The signaling pathways are regulating multiple mechanisms contributing to carcinogenesis including immune regulation. Microbiota is known to mediate development and regulation of immune system and therefore it can influence outcome of anticancer immunotherapy [48]. The role of microbiota and probiotics are also proposed in management of inflammatory and cellular immune response in COVID-19 [49, 50]. Moreover, the role of immune regulation in cancer and its management is a widely studied aspect. Antibodies against CTLA-4 are successfully used in anticancer immunotherapy but its efficacy depends on gut microbiota organisms *Bacteroides* spp. [51]. The role of commensal bacteria in influencing anticancer activity of immunotherapy is also reviewed [52] and it was suggested that normal intestinal microbiota supports anticancer therapy while this attribute is missing with dysbiotic microbiota and inflammation regulation is considered as an important mechanisms in this process [53]. For more than one century, inflammation is considered as a key mechanism for carcinogenesis after detection of leukocytes in cancer tissues [54]. Recent studies are also finding strong links between chronic inflammation and cancer risk

[55]. The microbiota components are known to up regulate several inflammatory cytokines and it has been reviewed in other articles [56]. Human functional genomics project indicated that fungal and bacterial agents are significantly associated with inflammatory cytokine response [57]. It is found that microbiota can promote cytokine production through engaging microbial metabolite sensor receptors that are highly expressed on inflammatory cells [58]. The study of antibiotic-mediated microbiota reduction and subsequent effects on pancreatic, colon, and melanoma tumor models revealed that microbiota depletion increases IFNγ producing T cell and reduces IL17A and IL10 producing T cell and reduces tumor burden in all models except Rag1-knockout mice [59]. IL-17 and IL-10 are considered as major immune regulators in a variety of carcinogenesis with a range of observations [60, 61], the role of microbiota in regulating these cytokines indicate towards their involvement in this process. Targeting of harmful microbiota components through antibiotics further boosts immune system and aids in suppression of cancer development. Several other bacteria are studied for their potential involvement in cancer with varied mechanisms. Among these, *Escherichia coli* is also found to be linked with colorectal cancer with a range of observations. It is found that increase of genotoxin producing microorganisms including *E. coli* can contribute to chronic inflammation-mediated colorectal cancer. It is suggested that colibactin induced host DNA damage contribute to colorectal cancer etiology [62]. Moreover, mutY is a DNA repair gene in *E. coli* and its human homolog MUTYH is linked with colorectal cancer. This homology of both DNA repair

genes and intracellular localization of *E. coli* in colonic epithelium during chronic inflammation raises suspicion that both DNA repair homologous proteins can compete and affect host cell DNA repair and therefore hypothesized for *E. coli*-mediated colorectal cancer [16]. Another well-studied bacteria for its involvement in carcinogenesis is *Fusobacterium nucleatum*, which is found to be implicated in colorectal cancer [63, 64], gastric cancer [65], esophageal cancer [66], and head and neck squamous cell carcinoma [67]. *F. nucleatum* is having certain regulators known to mediate cancerous changes, for example Fap2 protein of *F. nucleatum* interacts with TIGIT receptor present on natural killer (NK) cells and inhibit their cytotoxicity and subsequently contribute to tumor evasion [68]. Moreover, Fap2 also leads to *Fusobacterium* abundance in CRC which over-express Gal-GalNAc and binds to Fap2 protein, even though hematogenous route [69] and further contribute to its carcinogenic ability. Another *F. nucleatum* protein FadA bind to E-cadherin on CRC cells and induces β -catenin signaling leading to regulation of inflammatory and oncogenic response. This study also identified that synthetic peptide inhibit FadA—E cadherin-mediated CRC progression, inflammatory and oncogenic response and the level of FadA is also found to be higher in adenomas and adenocarcinoma than normal colon tissues [70]. The role of *F. nucleatum* in carcinogenesis is also reviewed and it has been suggested that its LPS can stimulate inflammatory cytokines leading to proinflammatory environment promoting tumor progression. The activation of ß-catenin signaling also activates Wnt signaling, Myc and cyclin D1 oncogenes contributing to cancer cell proliferation [71].

Another anaerobic bacterium *Peptostreptococcus anaerobius* selectively enriched in CRC microbiota. It is known to bind α2/β1 integrin (overexpressed on CRC cells) through putative cell wall binding repeat 2 (PCWBR2) surface protein present on bacteria. This interaction activate PI3K-Akt pathway through phospho-focal-adhesion kinase and stimulate increased cell proliferation, NF-kB activation and resultant proinflammatory events, such as interleukin-10, interferon-γ production and involvement of tumour-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), and granulocytic tumour-associated neutrophils (GTAM) [72]. The role of PI3K-Akt pathway is already suggested in several other microbes-associated cancer, such as *Salmonella typhi* is suggested to be involved in gallbladder carcinoma through this important pathway in addition to several other events [73].

Enteotoxigenic *Bacteroides fragilis* (ETBF) is another bacterium which produces BF toxin (BFT) contributing to diarrhea, inflammatory bowel disease and colon cancer [74]. BFT produced by ETBF promotes inflammation through expression of cyclooxygenase (COX-2) releasing PGE2,

activation of STAT3 signaling, and degradation of E-cadherin leading to upregulation of spermine oxidase-mediated DNA damage and carcinogenesis [75].

Porphyromonas gingivalis is found to be associated with increased pancreatic cancer risk. Though it is an oral bacteria but detected in human pancreatic cancer as an intracellular pathogen. Its intracellular residence is enhanced by hypoxia, which is an important characteristic of pancreatic cancer and intracellular persistence is directly related to increased tumor cell proliferation [76]. Some studies have indicated role of chronic *Mycobacterium tuberculosis* (Mtb) infection in lung cancer through induction of several mechanisms including inflammation [77]. It is demonstrated that Mtb induces lung specific cell dysplasia, squamous cell carcinoma. The Mtb-infected macrophages induces DNA damage in surrounding tissue and produces epiregulin (an epidermal growth factor) contributing to tumorigenesis [78]. *Salmonella enterica* subsp. *enterica serovar* Typhi (*S. typhi*) is also found to be linked with gall bladder carcinoma risk with its ability to form biofilm and production of toxin contributing to DNA damage and cell cycle alterations [79]. Similarly, *Helicobacter pylori* is a well-known bacteria recognized as carcinogen and contribute to carcinogenesis through multiple mechanisms. *H. pylori* induces inflammation, DNA damage, DNA methylation, epithelial mesenchymal transition, and direct cell proliferation through activation of various signaling events, like PI3K/Akt pathway [80]. These organisms are linked to certain diseases and do not form components of general microbiota, but their potentials in carcinogenesis provide indication of bacterial involvement in cancer progression.

Conclusion

The role of microbiota in cancer is a relatively new aspect and need more investigations to understand collective effect of microbiota components in carcinogenesis process. Discrete studies are arising understanding role of individual microbiota component in cancer progression, prevention and management. In contrast, microbiota works as an ecosystem where each component is contributing to the process of affecting normal host physiology. Therefore, we need a model to understand contribution of microbiota as a community in addition to understanding role of individual microbiota component in carcinogenic process. The recent development of next generation sequencing technologies with omics analysis can help us to develop such models. Several recent approaches such as microarray, metagenomics analysis coupled with meta-trascriptomics analyses can indicate about microbial community composition in addition to their influence on normal host physiology and subsequent effects on carcinogenesis. System biological approaches of

host–pathogen interactions analyses can also aid in these objectives through reducing time and labor required for such large-scale analyses of microbial community and their influence on disease progression [81–83]. Nonetheless, current findings and observations are indicating that microbiota can contribute to carcinogenesis through a variety of mechanisms and understanding of these mechanisms can help us to plan suitable preventive and therapeutic strategy for cancer. In addition, mechanistic identification of anticancer activity of microbes is paving the way to develop suitable therapeutics for management of cancer. Summarily, identification of mechanistic implication of microbiota in carcinogenesis and its prevention can provide us interventions for prevention and management of a variety of cancer.

Declarations

Conflict of interest The authors have declared no conflicts of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

Data availability All relevant data are available with manuscript.

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