Systematic Review

J. Biol. Regul. Homeost. Agents. 2023; 37(7): 3431–3454
https://doi.org/10.23812/j.biol.regul.homeost.agents.20233707.340

The Connection between Bacteria and Cancer: A Systematic Review of the Current Literature

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Published: 20 July 2023

Background: Outdated scientific literature claimed that bacteria was a cancerogenic agent. These studies were technically disfavored and the hypothesis of the role of bacteria in cancer was almost completely abandoned for many years. The aim of the present study was to investigate the role of microbiome in carcinogenesis and the potential role of engineered bacteria for the treatment of cancer.

Materials and Methods: The literature review was performed on Pubmed/Medline, EMBASE, Google Scholar database in accordance to the PRISMA Guidelines. The screening, and eligibility session was performed to conduct the data synthesis of the included studies.

Results: The screening process included a total of 415 papers, while 389 articles were considered for the eligibility session. A total of 334 scientific products were excluded and 55 articles were considered for the descriptive synthesis. Recent reports, however, have produced new results on the role of various microorganisms in tumors. Here, we reviewed the scientific literature on this issue in order to provide an updated organic framework on the topic.

Conclusions: Although basic research studies investigated and confirmed the role of bacteria in cancer induction, maintenance and resistance to therapy, the more recent literature is oriented to modern diagnostic approaches from the basic scientific knowledge to the clinical practice. The approaches to biological and immunological onco-therapy, by natural or bioengineered bacteria, were also addressed.

Keywords: microbes; cancer; microbiome; microbiota; cancer causes; diagnosis; therapy; immunotherapy; biological based therapy

Introduction

In today's society, cancer is still perceived as a disease generated by somatic mutations of cells, whereas the contribution of infectious agents in its pathogenesis is considered a rare exception, limited to few cancers histotypes and cases [1]. However, new literature reports guided us to better focus on the infectious physiopathology of tumorigenesis [2,3]. In fact, high quality studies have credibly demonstrated that certain microbes are directly implicated in tumor formation, while others are synergic agents in tumor maintenance and resistance to therapies [4,5]. Certain microbes have also been implicated in modulating the immune properties of tumors, contributing to their pathological immune tolerance [6–13].

To date, eleven bacterial strains are known as oncomicrobes, classified by the International Association for Cancer Registries (IACR) [6,14]. These oncomicrobes are responsible for about 2 million cases per year globally (around 13% of global cancer cases). Their epidemiology, molecular mechanisms and clinical studies have been extensively reviewed [15]. Among them, there are common germs causing genotoxin-mediated mutagenesis through specific molecular effectors like colibactin (a DNA alkylator), cytolethal distending toxin (CDT) or bacteroides fragilis toxin (Bft) [16,17], bacterial virulence factors like FadA from Fusobacterium nucleatum and AvrA, which act through E-cadherin–Wnt–b-catenin signaling [18]. In addition to these direct oncomicrobes, complicit oncomi-

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Table 1. Screening strategy and database search.

	Search Strategies
Keywords search:	Advanced keywords search: (microbiology [Subheading] OR "bacteria" [MeSH Terms] OR bacteria [Text Word]) AND (neoplasms [MeSH Terms] OR cancer [Text Word])
Timespan	[2019–2023]
Electronic Databases	Pubmed/Medline, EMBASE, Google Scholar

crobes generate molecular effectors promoting carcinogenesis [19–21]. Gallic acid, for instance, is a bacterial metabolite able to activate carcinogenesis caused by *p53* mutations [21]. Other germs can contribute to fatal drug resistance in certain tumors, by producing specific drug resistance factors like those conferring gemcitabine resistance in pancreatic cancer [22]. Bacteria can indirectly favor tumor development and resistance by acting as immunomodulators. For instance, commensal lung microbiota promotes expansion and activation of T cells, driving tumor-promoting inflammation through local interleukin-17 (IL-17) and IL-23 release, facilitating Kras mutations and *p53* loss carcinogenesis [21,23]. Gut bacteria producing secondary bile acids reduce hepatic sinusoidal CXCL16 expression and prevent CXCR6 mediated natural killer T cell aggregation, compromising immunosurveillance in liver cancer formation [24].

Despite solid scientific knowledge on the role of microorganisms in cancer pathogenesis, the search for cancer related bacteria is not routinely performed on patients in common clinical practice. This is essentially due to technical challenges faced when trying to identify cancer-related germs in an extraordinarily complex biological background such as that of a human body, hosting more than 4×10^{13} microbial cells spanning ~3×10^{3} species, plus *archaea*, *eukarya* (including fungi), viruses and phages [25]. Standard culturing techniques would invariably lead to misleading results [26], as it famously happened in historical experiments conducted by Thomas Glover and Virginia Livingston-Wheeler [27,28]. Recent diagnostic approaches address the role of bacteria in cancer patients taking advantage of much more advanced diagnostic techniques, instead. These studies were performed mostly on the human gut [29,30], but also on other organs' microbiota [4,7,23,31–35], and could clearly identify significant contribution of germs to cancer initiation, maintenance and response to therapy [36,37] in patients cohorts. We review these diagnostic studies with the hope that excellence techniques can soon be translated from excellence centers to other clinical centers worldwide. To complete the literature framework linking bacteria and cancer, here we also review the current biological and drug-based approaches against oncomicrobes, i.e., therapeutic strategies that, employing wild-type or genetically engineered bacteria as anti-cancer agents and further combinations of bacteria and nanomaterials, are able to provide an almost infinite spectrum of possibilities to be tested for bacterial based approaches to cancer therapy [38]. The aim of the present investigation was to evaluate the relationship between the development of human neoplasms and bacteria through a systematic review of the literature.

Materials and Methods

Database Screening

The entire systematic review process is available on NIHR website (prot. n. 450681). The screening process, eligibility criteria assessment and data synthesis search was performed in accordance to the Standards for Reporting Qualitative Research (SRQR) and PRISMA guidelines (**Supplementary File 1**). The Boolean keyword strategy has been fully summarized in Table 1. The screening process was performed and updated up to February, 20th 2023 applying a timespan ranged between 2019–2023. The following PICO question was considered:

P = Population/Patient/Problem—Patients affected by cancer;

I = Intervention—Therapy/adjuvant supplement effect on Microbiome/bacteria assessment;

C = Comparison—None;

O = Outcome—Clinical Effectivenesses and major complications.

Inclusion/Exclusion Parameters

The preliminary phase was performed considering the evaluation of the abstract and title search applying the following inclusion criteria: randomized clinical trials (RCTs), non-randomized clinical trials (non-RCTs), prospective and retrospective studies. The following exclusion criteria were considered: literature systematic reviews, editorial letters, articles in non-English language, case reports and case series, *in-vitro* experiments and clinical studies still in progress. The scientific contribution included were considered for further full-text assessment.

Selection Procedure

The entire eligibility process was performed independently by two reviewers based on the full-text evaluation (FL and AS). For all scientific publications in duplicates and excluded articles the exclusion reasons have been reported.

Data Assessment

The study data were collected using a dedicated electronic database by the Excel software package (Office 365, Microsoft, Redmond, WA, USA) in accordance to the fol-

lowing sub-categories: authors, journal, years of publication, study design, anticoagulant protocol, subjects, type of cancer, grading/severity, site/organ, type of bacteria, intervention/adjuvant supplement, follow-up.

Results

The entire process of the scientific products screening, eligibility process and data synthesis were summarized in Fig. 1. The scientific contributions included were 415 articles while a total of 8 duplicates were excluded. After the preliminary evaluation, a total of 34 papers have been excluded and 389 scientific products have been considered for the full-text assessment and eligibility evaluation process. A total of 334 articles were excluded according to the following reasons: 329 articles that did not fulfill the study topic, 1 paper that described a wrong outcome, 4 studies still in-progress. At the end of the process, a total of 55 scientific contribution were included and considered for further synthesis and descriptive data analysis (Tables 2,3,4,5,6,7,8, Ref. [39–71]).

Discussion

Diagnostic of Cancer Microbes

Contamination and irreproducibility problems plaguing research relying on culturing techniques during the early 20th century remain a challenge even today for microbially based cancer diagnostics (Table 2). Nevertheless, well conducted recent studies have shown that cultivable bacteria are indeed present in breast [72,73], lung [21], prostate [72], pancreas [1], and colon cancers [74]. *S. gallolyticus* bacteremia has been reported to provide a clinical indicator for the status and type of host tumor due to its presence [75,76]. Genetic sequencing conducted on cancer originated in the aerodigestive region [77], colorectal tract [78–80], pancreatic tumors [81,82] and lung cancer [83,84] defined a clear contribution provided by the microbiome in different cancer models. In-depth functional analyses and multi-omic tools have started to elucidate functional interactions between microbes, the immune system and cancer cells [85,86], and to provide solid technological platforms for the development of innovative clinical diagnostic approaches in oncology practice. A recent multicenter trial reported clear findings regarding a specific intratumoral microbiome patterns in more than 30 tumor models and 7 cancer types by a blood-based method of investigation [4]. In the present investigation, the authors evaluated a specific region of 16S rRNA amplicon sequence, quantitative PCR, lipopolysaccharide (LPS) and lipoteichoic acid (LTA), immunohistochemistry assessment, cell culture and electron microscopy, assessing the bacterioma obtained by a sample size of 1010 tumors including skin tumors and melanoma, lung neoplasms, ovarian, nervous system, pancreatic cancer, bone tissues, and breast neoplasms. The same authors investigated a total of 811 experimental controls, through DNA extraction, qPCR, and paraffin embedding. Then, a total of 94.3% bacteria was identified and removed as contaminants. The quantitative PCR was performed to assess the bacteria charge per tissue section. The authors concluded that the genomics techniques could be a useful tool for a bacteria-based neoplasm diagnosis [4]. Moreover, Poore *et al*. [32] obtained, in a large sample study, treatment-naïve whole-genome and transcriptome data from a total of 18,116 samples obtained from a total of 33 neoplasm types present in The Cancer Genome Atlas (TCGA) in order to evaluate the bacterial, viral and archaeal nucleic acids. In conclusion, the researchers removed more than 91.3% of microbial taxa as contaminants [35]. A machine learning approach was considered as a highly predictive tool for in cancer discrimination. This IA technology is able to potentially produce an efficient tumor diagnosis, to find neoplasm-specific microbiota patterns through the analysis of plasma-derived microbial DNA obtained from a total of 100 subjects affected by lung cancer, prostate or melanoma neoplasms and compared to a total of 69 HIV-negative, healthy patients [74,87] (Table 2). Several meta-analyses conducted on public cancer datasets characterized by a uniform host depletion, decontamination procedures and isolation, taxonomy and functional profiles were able to indicate certain microbial drivers in tumor development, physiopathogenesis and clinical treatment [76,88,89]. On the other hand, these investigations reported significant findings concerning the genomic protocols as useful tools for the microbial contribution determination in the neoplasms development, some determinant technical issues emerged in consideration of the specificity, prevalence and stability during the neoplasms treatment or utility during antibiotic administration. These issues need further investigation prior to a large-scale application of these protocols as a potential gold standard procedure. Moreover, a comparative assessment of the blood samples obtained by subjects affected by non-lethal bodily infections, septic patients and subjects under antibiotics administration during cancer care needs preliminary screenings to use for comparison [4,90].

Gut Microbiome

The intestinal barrier represents the widest host-bacterial interface and the largest microbiome diversity (Table 3). The current studies are oriented towards the potential microbiome impact on the oncogenesis or neoplasms prognosis considering the key role played by the gut microbiota [91,92]. The gut microbiome is able to regulate a wider spectrum of functions concerning the tumor-bearing organism, typically through the biochemistry influence and immunomodulation [75,76,93]. These factors are a key component of the immuno-oncology-microbiome axis, an immune-mediated interaction and feedback interaction loops. The microbiome interactions are able to induce a considerable effect on non-hematopoietic and hematopoi-

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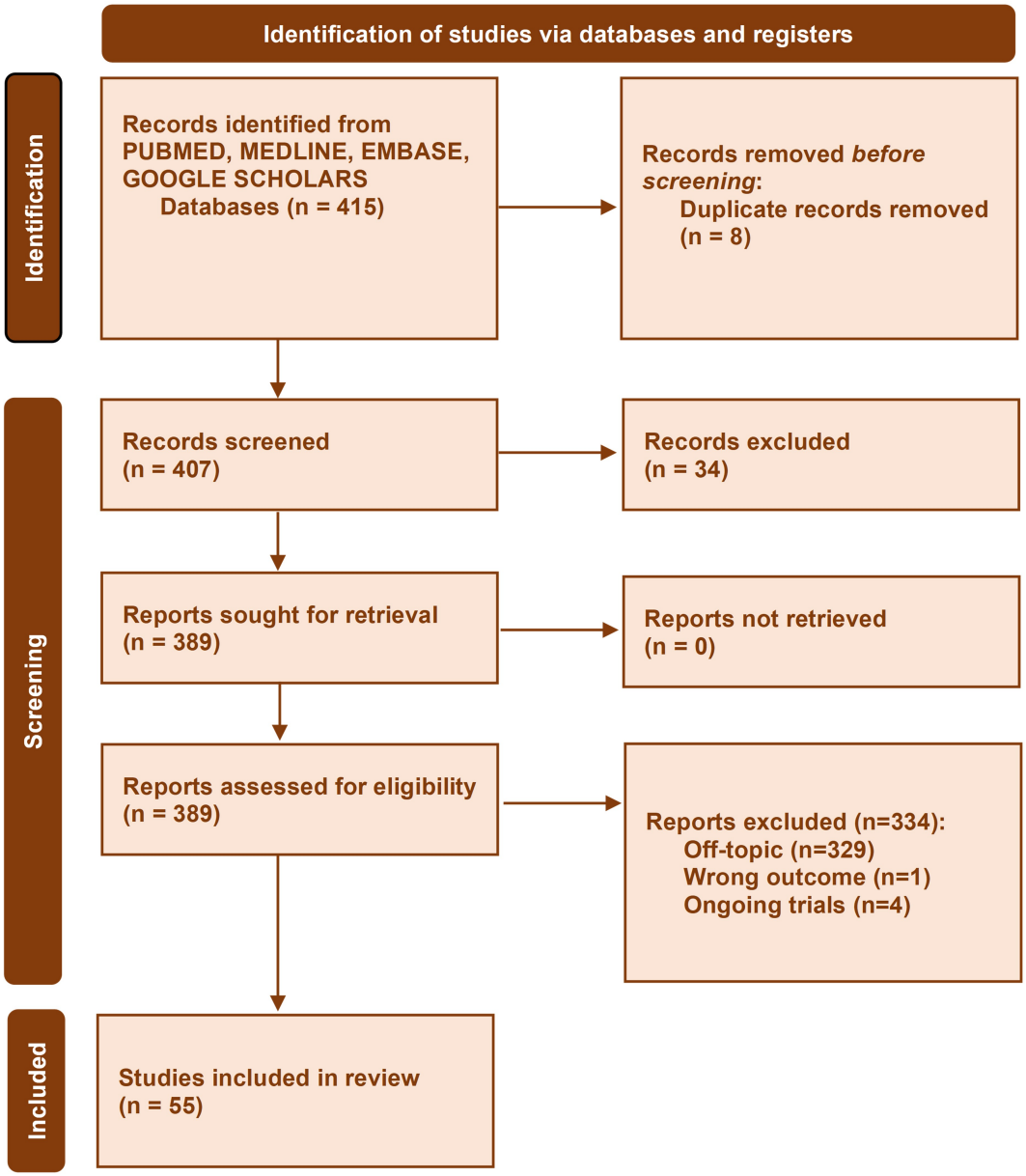

Fig. 1. Article screening process and analysis according to the PRISMA workflow.

etic factors of the gut-epithelial barrier, a modulation both of primary and secondary lymphoid function and at the same time a regulation of the immune tone of the cancer microenvironment (TME). The intestinal environment is able to produce a significant effect on cancer both locally and at distance from the neoplasia altering the immunity context, influencing the myeloid and lymphoid cells, and inflammatory and metabolism pathways. As a study finding, immune recovery after hematopoietic stem cell transplantation is able to influence the clinical relapse and transplant-related subject mortality [88,91]. This dynamic has been strictly correlated to gut microbiome composition [94]. A recent multicenter, multinational clinical trial reported that a higher intestinal microbiome diversity is significantly correlated to a lower patient mortality after allogenic HSCT [95]. Moreover, important correlations between the gut microbes composition, dietary characteristics, post-transplant bone marrow, thymic cell activity, lymphopoiesis and myelopoiesis have been detailed and documented in mice [91]. Moreover, the gut microbes depletion is able to influence the infection clearance after bone marrow tissue transplantation. Specific microbes-derived compounds are able produce an immunity protection against the damage on hematopoietic tissues induced by irradiation therapy [94,96–99] through the propionate and tryptophan release or through the release of MAMPs. This process is able to improve the bone marrow-derived myeloid cells and neutrophil activity [75,100]. This effect could be partially

Table 2. Summary table of cancer microbes diagnostic.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grade	Site	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Zaharuddin *et al*. [39]	BMC gastroenterology	double-blind RCT	2019	52 patients	colorectal cancer	Duke's C colorectal cancer	Gut	(1) Lactobacillus acidophilus (2) Lactobacillus lactis (3) Lactobacillus casei (4) Bifidobacterium longum (5) Bifidobacterium bifidum (6) Bifidobacterium infantis	Probiotics	Probiotic are able to modify intestinal environment producing a decrease of pro-inflammatory cytokines after surgery.	4 weeks
Li *et al*. [40]	BMJ	blinded RCT	2019	3365 patients	Gastric cancer	1107 H pylori sieric antibody/Negative	Stomach	Helicobacter pylori	(1) H pylori treatment with amoxicillin and omeprazole for two weeks (2) vitamin (C, E, and selenium) (3) garlic supplementation for 7.3 years	H. pylori treatment give a protection effect in gastric cancer incidence over then 22 years post-surgery with a significant decrease of cancer mortality.	7.3 years
Amanati *et al*. [41]	BMC infectious diseases	retrospective study	2021	2393 patients	hematological/solid organ tumors	-	multi-organ	bloodstream bacteria infections	blood coltures	High proportion pathogens were connected CR and ESBL-producing Enterobacterales and Pseudomonas spp.	4 years
Goggin *et al*. [42]	JAMA oncology	prospective pilot cohort study	2020	47 patients	hematological/solid organ tumors	Pediatric subjects With Relapsed or Refractory Cancer	multi-organ	bloodstream bacteria infections	blood coltures	mcfDNA-seq is able for a clinical identification of pathogens days before the onset for an early treatment.	1 year
Bingula *et al*. [43]	Respiratory research	CT	2020	18 patients	non-small cell lung cancer	-	Lungs	Salivary microbiota	16S rRNA gene sequencing	Increased abundance of Firmicutes in LL, with a decrease of Proteobacteria.	-

RCT, randomized controlled trial; CT, clinical trial.

Table 3. Summary table of gut microbiota modification in cancer development.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
So *et al.* [44]	Nutrients	RCT	2021	40 patients	colorectal cancer	high risk of colorectal cancer (grade 4–7)	Gut	Firmicutes, Bifidobacteria, Prevotella_9, Lactobacillales and Bacilli	Rice Bran Dietary	A 24-week rice bran dietary is able to ameliorate the health through an impulse of the intestinal microbiota.	24 months
de Clercq *et al.* [45]	Clinical cancer research	double blinded RCT	2021	24 patients	Gastroesophageal Cancer	metastatic HER2-negative gastroesophageal cancer	Esophagus/Stomach	Gut microbiota	Fecal Microbiota Transplantation	FMT did not affect cachexia, but could produce an increased response and survival in subjects affected by gastroesophageal metastasis.	1 year
Martini *et al.* [46]	International journal of cancer	single-arm CT	2022	62 patients	solid organ tumors	metastatic colorectal cancer chemorefractory nonsmall cell lung cancer	Gut/Lungs	Gut microbiome		Agathobacter and Blautia expression in fecal samples are associated to a higher progression-free survival.	24 months
Byrd *et al.* [47]	Journal of experimental medicine	CT	2021	1359 patients	non-gastrointestinal cancers.	-	multi-organ	Gut microbiome	-	Bacterial species shift across decades of life Bacteroidota spss. increased with age. Actinobacteriota spss decreased with age.	-
Biehl *et al.* [48]	PLoS ONE	cohort study	2019	41 patients	hematological/solid organ tumors	-	multi-organ	Gut microbiome	-	High recurrence of Enterococcaceae Enterococcus (90 samples, 22.2%) on genus level. High quantity of skin commensals in 99 samples.	-

Table 4. Summary table of extraintestinal microbiota in cancer development.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Mollee *et al.* [49]	Journal of hospital infection	non-blinded CT	2020	640 patients	solid organ tumors	Adult cancer patients	multi-organ	bloodstream infections	-	Catheter-associated bloodstream infection in subjects affected by cancer was not impacted by whether central venous access devices insertion.	-
Newman *et al.* [50]	Scientific reports	cross-sectional study	2019	49 patients	squamous cell carcinoma (HNSCC)	-	head/neck	Oral microbiome	marijuana usage	At the level of the tongue, genera earlier shown to be enriched on HNSCC mucosa, Capnocytophaga, Fusobacterium, and Porphyromonas, reported at decreased levels in subjects with marijuana consumption, and the Rothia was increased.	-
Huang *et al.* [51]	International journal of radiation oncology	CT	2021	445 patients	Carcinoma	Nasopharyngeal cancer	head/neck	Nasopharyngeal Commensal Microbiome	Radiation Therapy	A stable change was detected in the nasopharyngeal microbiota in subjects with NPC under radiation treatment.	3 months

Table 5. Summary table of intratumor microbiota in cancer development.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Watanabe *et al*. [52]	Scientific reports	RCT	2020	223 patients	colorectal cancer	-	Gut	Escherichia coli	Nutrient Intake	Gut polyketide synthase is deter, omamt in colorectal cancer development.	-
Sun *et al*. [53]	Integr Cancer Ther	RCT	2020	40 patients	colorectal cancer	stage IV metastatic colorectal cancer	Gut		Quxie-TCM herbs	Escherichia-Shigella decreased both in Test and control groups. Faecalibacterium were higher in control group. Prevotella was higher in test group.	1 month
Reuvers *et al*. [54]	British journal of surgery	RCT	2023	485 patients	colorectal cancer	-	Gut	Proteobacteria	-	Proteobacteria sensitizes patients to infection and worsens outcome after sepsis.	-
Cornejo-Juárez *et al*. [55]	Current HIV research	CT	2020	40 patients	AIDS-deèendent malignancies	Disseminated Kaposi sarcoma (DKS)	multi-organ	Mycobacterium avium complex	Bone Marrow Culture	Mycobacterium avium complex was recognized in bone marrow cultures.	-
Wang *et al*. [56]	Journal of ovarian research	CT	2020	16 patients	ovarian cancer	-	ovaries	Ovarian microbiome	cancerous and noncancerous ovarian tissues	The cancerous ovarian bacteriome reported an increased quantity of Aquificae and Planctomycetes and lower level of Crenarchaeota.	2 months
Shibata *et al*. [57]	PLoS ONE	CT	2021	20 patients	cervical cancer	-	Cervix	cervical microbiome	liquid-based cytology	HPV16 was significantly correlated with community types that were not dominated by Lactobacillus strains.	2 years
Ravilla *et al*. [58]	Integrative cancer therapies	CT	2019	31 patients	Cervical Squamous Intraepithelial Lesion	High grade	Cervix	cervical microbiome	Human Papillomavirus Therapeutic Vaccine	The bacteria taxa in the cervix may be enriched in non-responders subjects.	-

Table 6. Summary table of antimicrobial strategy for cancer treatment.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Prizment *et al*. [59]	Alimentary pharmacology & therapeutics	double-blind RCT	2020	50 patients	colorectal cancer	High risk of colorectal cancer	Gut	Prevotella, Veillonella, Clostridium XlVa and Clostridium XVIII clusters	oral aspirin 325 mg daily vs. placebo	Aspirin intake is able to influence many different bacteria taxa.	6 weeks
Choi *et al*. [60]	The New England journal of medicine	double blinded RCT	2020	3100 patients	Gastric cancer	History of gastric cancer, peptic ulcer, or other organ cancer; previous H. pylori eradication therapy	Stomach	Helicobacter pylori	Lansoprazole [30 mg], amoxicillin [1000 mg], and clarithromycin [500 mg], twice daily for 7 days	H. pylori eradication protocol is able to decrease the risk of gastric cancer.	9.2 years
Yan *et al*. [61]	Gastroenterology	RCT	2022	1676 patients	Gastric cancer	High-risk population for gastric cancer	Stomach	Helicobacter pylori	H. pylori eradication therapy	H pylori eradication treatment reduced the gastric cancer risk increasing the benefit effects expecially in subjects with no precancerous lesions.	26.5 Years
Sung *et al*. [62]	Gut	RCT	2020	587 patients	Gastric cancer	H. pylori-positive patients	Stomach	Helicobacter pylori	H. pylori eradication therapy vs. placebo	A. lwoffii, S. anginosus and Ralstonia increased with the treatment. Oral bacteria such as Peptostreptococcus, Streptococcus, Parvimonas, Prevotella, Rothia and Granulicatella were correlated to gastric atrophy and metaplasia.	1 year
Poonyam *et al*. [63]	Asian Pacific journal of cancer prevention	double blinded RCT	2019	100 patients	Gastric cancer	H. pylori-positive patients	Stomach	Helicobacter pylori	High-Dose PPI- Bismuth-Containing Quadruple Therapy with/without probiotics	The therapy combined with probiotics is able to produce the 100% eradication with antibiotic resistance.	14 days
Noda *et al*. [64]	PLoS ONE	retrospective study	2021	432 patients	Gastric cancer	Resection with and without Helicobacter pylori eradication	Stomach	Helicobacter pylori	H. pylori eradication therapy	Different NE were reported in gastric cancer, and the internal surface NE type was significantly correlated to H. pylori-free cancer.	

Table 6. Continued.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
MacManus *et al*. [65]	European journal of cancer	RCT	2021	70 patients	non-gastric marginal zone lymphoma (MZL)	Stages I and II or paired-organ, non-gastric MZL	Stomach	Helicobacter pylori	radiotherapy	Radiotherapy was reported as a curative protocol with decreased toxicity in localised non-gastric marginal zone lymphoma.	
Kim *et al*. [66]	Clinical and translational gastroenterology	RCT	2020	72 patients	Gastric cancer	Clarithromycin Resistance-Helicobacter pylori (mutations in 23S rRNA)	Stomach	Helicobacter pylori	Tailored therapy [triple or quadruple therapy with esomeprazole, metronidazole, tetracycline, and bismuth/10 days]	Tailored therapy based is a good option to increase the eradication rates in case of higher prevalence of antibiotic resistance.	10 days
Schmelz *et al*. [67]	Journal of gastroenterology	prospective study	2019		MALT lymphoma	low-grade stages IE and II1E	Stomach	H. pylori	Antibiotics and radiation therapy	In refractory patients or H. pylori- low grade gastric MALT lymphoma a dosage-reduced radiation therapy was effective in stage IE and II1E.	2.8 months
Maarbjerg *et al*. [68]	Journal of pediatric hematology/oncology	CT	2022	196 patients	solid organ tumors	Pediatric subjects	multi-organ	bloodstream bacteria infections	piperacillin-tazobactam and meropenem	Gram-positive BSIs, and stable, low-resistance rates against currently recommended empirical antibiotics, piperacillin-tazobactam and meropenem.	10 years
Yamashita *et al*. [69]	Pharmacological research	CT	2022	54 patients	solid organ tumors	obstructive jaundice	multi-organ	bloodstream bacteria infections	Inchinkoto	Inchinkoto positively correlated with Clostridia but negatively correlated with Lactobacillales.	1 year

Table 7. Summary table of prebiotics/probiotics supplemements for cancer treatment.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Gniadek *et al*. [70]	Journal of immunotherapy	CT	2020	22 patients	colorectal cancer	metastatic carcinoma	Gut	Salmonella typhimurium attenuated strain with human gene interleukin-2 (10^{10} CFU)	Saltikva	Higher circulating natural killer (NK) cells and NK-T cells compared to the baseline.	11 weeks
Hassan *et al*. [71]	Clinical cancer research	open-label phase Ib study	2019	35 patients	Pleura	unresectable Malignant pleural mesothelioma	Lungs	Live-Attenuated, Listeria monocytogenes (CRS-207) with Chemotherapy	CRS-207 and chemotherapy	Combination of CRS-207 and chemotherapy is able to produce a significant positive effect in the local cancer environment.	5 months

Table 8. Summary table of bacteria supplemements for cancer treatment.

Authors	Journal	Study type	Year	Subject(s)	Type of cancer	Grading/Severity	Site/Organ	Bacteria(s)	Adjuvant supplements/Intervention	Main findings	Follow up
Gniadek *et al*. [70]	Journal of immunotherapy	CT	2020	22 patients	colorectal cancer	metastatic carcinoma	Gut	Salmonella typhimurium attenuated strain with human gene interleukin-2 (10^{10} CFU)	Saltikva	Higher circulating natural killer (NK) cells and NK-T cells compared to the baseline.	11 weeks
Hassan *et al*. [71]	Clinical cancer research	open-label phase Ib study	2019	35 patients	Pleura	unresectable Malignant pleural mesothelioma	Lungs	Live-Attenuated, Listeria monocytogenes (CRS-207) with Chemotherapy	CRS-207 and chemotherapy	Combination of CRS-207 and chemotherapy is able to produce a significant positive effect in the local cancer environment.	5 months

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associated to the release of endogenous ligands for RIG-I viruses, phages or bacteria that could produce IFN-I pathways signal in enterocytes to achieve intestinal barrier repairing [101]. Recent studies highlighted the role of the gut microbiome also on the adaptive immunity [26], where anticancer immunotherapies produce evident correlations between distinct commensals and protective anti-tumor T cell responses. For instance, in the case of cyclophosphamide therapy, the *Enterococcus hirae* was able to translocate and stimulate pathogenic helper T cell 17 (TH17) activity and IFN-producing CD8+ T cell effectors that are correlated to the cancer growth in sarcoma and lung adenocarcinoma [102,103]. Moreover, in subjects affected by melanoma, cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) blockade is correlated to fecal relative enrichment of *Bacteroides thetaiotaomicron* and *B. fragilis* that mediated Toll-like receptor 4 (TLR4)– and IL-12–dependent TH1 responses with the therapy effectiveness [104]. The inhibition of PD-(L)1 ligand is able to induce T-cell priming in melanoma cancer and it was effective for harboring *Bifidobacteria* spss, detectable in microbiota [105]. Adoptive T-cell transfer effectiveness in melanoma cancer in the case of total body irradiation is strictly determined by microbiota composition, the gut microbes translocation and TLR4 patterns [106]. Oxaliplatin-drug is able to induce the death of ileum enterocyte cells and it is able to inversely determine the immunogenicity of *Erysipelotrichaceae* and the tolerogenicity of *Fusobacteriaceae* in the ileum region, balancing of the anticancer follicular T-helper and deleterious TH17 activity in colon neoplasms [2]. GALT-Dendritic cells obtained from spleen/tumor lymph node indicated several different commensals including *Bifidobacterium spp.*, *B. fragilis*, *A. muciniphila*, *B. rodentium*, *Bacteroidales S24-7* able to catalyze and modulate the immunity activity by IFN-I and IL-12 signal paths [107,108]. The gut microbiota represents a key antigen source that could produce a significant specific response of T cells, also systemically [109], and provide dendritic cell adjuvants able to produce an immunological boosting effect. On the other hand, the commensal-specific immunological response is also able to induce negative or protective host effects. Gil-Cruz *et al*. [107] reported that the homology associated to *B. Thetaiotaomicron*–derived b-galactosidase and host cardiac myosin heavy chain 6 is able to induce a lethal autoimmune inflammatory cardiomyopathy. Hebbandi Nanjundappa *et al*. [108] described that a cross-reactivity action between Bacteroides integrase and host IGRP is able to induce self-reactive CD8+ T cells to suppress colitis. Molecular mimicry mechanisms between neoplasm development and microbiome antigens have been assessed and evaluated for those purposes [110,111]. For instance, a H-2Kb–restricted T cell immune response against a specific phage of enterococci strains (*E. hirae*) was also able to cross-react with an oncogenic driver (PSMB4). In fact, an oral administration of *E. hirae* strains with this phage could improve the phage-specific T cell activity against extraintestinal neoplasms over-expressing PSMB4 with a cyclophosphamide or anti–PD-1 antibodies theraphy [111]. Similarly, T cells targeting an epitope, SVYRYYGL (SVY), expressed in the commensal strain of *Bifidobacterium breve*, cross-reacted with a model neoantige SIYRYYGL (SIY), expressed by mouse melanoma B16-SIY [111,112] (Table 3). Some lines of human T-cells are specific for naturally processed skin melanoma cancer and they appear to recognize bacteria peptides [112]. This process seems to suggest a useful clinical relevance for therapeutic oncological purposes. Several different mechanisms able to induce significant effects on the anti-neoplastic immunological response are suggested. In fact since Nomura *et al*. [113] reported that a combination of 11 different bacteria was able to increase the level of cancer antigen–specific CD8+ IFN-g+ T cells associated to an immunity checkpoint not cross-reactive blocking with microbial antigens not originated by the colon. Gut metabolites are able to produce a significant modulation of the immune response. In this way, the tumor radiotherapy was more effective if combined with vancomycin administration to eradicate Clostridiales-derived metabolites including the butyrate and propionate, that were associated to the higher DC antigen presentation and CD8+ T cell priming [113]. On the other hand, gut microbial propionate and tryptophan path metabolites (such as 1H-indole-3-carboxaldehyde, kynurenic acid) were reported to produce a long-term radioprotection *in vivo* [114]. Higher blood butyrate and propionate activity were associated to an increased CTLA-4 blockade resistance in mouse models and patients affected by skin melanoma cancer, through an increased regulatory T cell ratio, reduced DC and effector T cell activation, and lower IL-2 responses [115]. These mechanisms were associated to a longer progression-free survival occurring with the anti–PD-1 theraphy [116]. Moreover, an increased *A. muciniphila* outgrowth has been reported in an *ex-vivo* investigation able to decrease the melanoma progression through a T cell–dependent path, decreasing the IL-6, IL-1a, IL-10, IL-17A and IL-23 cytokines serum level. In another study, the prebiotic inulin was demonstrated to induce the increase of *Bifidobacteria* spss. in the intestines through several different mechanisms, to boost the cytotoxic T lymphocyte functions in spleen and increase the melanoma resistance to MEK inhibitors [117,118]. The main compounds also include butyrate and niacin and they are able to modulate IL-18 in colon tissues via a Gpr109a-dependent induction and they are able to suppress colitis and neoplasms of the colon [115, 119]. Moreover, the myeloid-cell reactive oxygen species (ROS) release is decreased by antibiotic theraphy or germ-free status, that is able to decrease the oxaliplatin-drug capability to modulate the early cancer genotoxicity [116,119–121]. Microbes could be involved in cancer promoting capabilities and induce the transformation of xenobiotics and tumor drugs, due to non-completely known effects on ther-

apy and prognosis. For example, abiraterone acetate was reported in prostate neoplasms as a consistent source of energy for *A. muciniphila,* while it resulted in an inhibition of *Corynebacterium* species through on AA-inhibited androgens for the growth [121]. Due to the anti-inflammatory properties of the *A. muciniphila*, the pro-inflammatory action was performed by *Corynebacterium* species. These alterations regarding the relative abundances of the bacteria species were able to improve the pharmacologic efficiency of the abiraterone acetate therapy. The *A. muciniphila*'s immunomodulatory action [106,122], including association with responders during PD-1 blockade [123], seems to support the hypothesis that increased levels of *A. muciniphila* could be supportive regarding the abiraterone acetate efficiency in androgen-independent prostate tumors [124], although this aspect needs larger population sample cohorts to be tested *in vivo*. A specific disquisition should be provided about the role played by the secretome. In this way, the secretory components should be deeply considered concerning the role played by the bacteriome in neoplasm progression. For this purpose, outer membrane vesicles (OMVs) have been reported to reprogram the TME by an immunological pro-tumorigenic path of tumor associated macrophages [125]. Despite gut microbiota modulation in murine immuno-therapy models reported very promising findings, these results have not been applied to commercial therapeutic protocols in human oncology (Table 3). In fact, recent studies on gut microbes conducted on humans and mice models seems to support that a stratified therapy response, including the immunotherapy [126], reported no varying taxonomic differences although there is a strong concordance about the functional profiles [127].

Extraintestinal Microbiota

Extraintestinal cancer is able to develop and progress within tissues that harbor their own microbiome, and this microbiome could play a key role in the cancer exacerbation process (Table 4). Recent studies performed in lung tumors in mice models showed that local bacterial commensals could be consistently altered by carcinogenesis events. The mechanism of action seems to be associated with a tumor progression impulse and correlated to the inflammatory cross-talk played by the alveolar macrophage lines and the IL-17–producing lung T cells [128,129]. The relevance of this finding has been recently confirmed in a total of 83 subjects affected by lung neoplasms. Tsay *et al*. [34] reported that the local microaspiration of supraglottic bacteria in subjects affected by lung neoplasms could significantly condition the response to the therapy and the survival rate. This process seems to be associated to an immunity checkpoint inhibition associated to TH17–mediated inflammation pathway [36]. The skin is also known as the largest and outermost organ, with a key role for the host homeostasis maintenance by tight interconnections between the commensal bacteria, keratinocytes and skin immune components by a complex network of metabolic, innate and cognate immune activity [130]. Compositional shifts of the skin microbiome seem to condition non-melanoma skin carcinogenesis [131]. Cervical neoplasms induced by high-risk HPV infection is similarly correlated to an altered cervical microflora [97,132]. A brief disquisition is necessary to highlight the complex network of interactions played by the bacteria with the enteric system. Recently, it was confirmed in literature that microbiota-responsive neurons could produce a consistent influence on the metabolism control avoiding the central nervous system control [122], and concerning not only the stromal, neoplastic, endothelial cellular component and hematopoietic progenitor–derived compounds, but also a dense network of adrenergic nerve fibers that could produce a significant influence on the tumor development in brain and non-brain neoplasms [133–135]. Due to these considerations, further clinical trials are necessary to investigate the interactions between mucosal or tumoral commensals and tumor innervation (Table 4).

Intratumor Microbiome

Recent studies conducted on living bacteria have been assessed by different tumor types outside the aerodigestive tract and they reported no significant evidence in literature [136] (Table 5). Intratumor bacteriome have been reported to produce a significant neoplasms-specific effect on: (1) gastric, intestinal and urinary tract carcinogenesis through secreted genotoxins, most notably pks+ *Escherichia coli*–derived colibactin and *B. fragilis*–derived toxin [137]; (2) CagA-mediated or IL-17–producing gd T cell–mediated inflammation in stomach and lung cancers, respectively [17]; (3) a chemo-resistance interaction through a direct action on the microbes metabolism in pancreas neoplasms or cancer cell by autophagy indirect amplification in colorectal tumors [88]; (4) neoplasm proliferation by a fungi activation of the host's C3 complement cascade in pancreas tumor [36]; (5) metastasis by an up-regulation of tumor matrix metalloproteinases in breast neoplasm or by anticancer immunosurveillance decrease in lung [14,72]. Moreover, it has been reported that gut microbiome could alter the intratumoral microbiome composition in pancreas neoplasms, probably by the pancreatic duct communication [36,38] (Table 5).

Therapeutical Strategies

In literature, a definite and conflicting correlation regarding the use of antibiotics in solid tumors was reported (Table 6). However, antibiotics have been administered to control *H. pylori*–derived gastric lymphomas through a triple or quadruple antibiotic administration protocol. The administration of antivirals drugs against active hepatitis C virus and vaccination against major HPV serotypes and HBV has been purposed in order to avoid urogenital, cervical, head and neck and liver neoplasms [138]. In some studies, antibiotics seem to contrast the immunother-

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apy response by inhibiting the gut microbiome [139], but paradoxically they can also increase the immunotherapy effectiveness through an upregulation of the PD-1 expression in case of pancreatic intratumoral microbiota elimination [38]. Many studies conducted on subjects affected by lung, colorectal cancer, and pancreas neoplasms reported that the eradication of the intratumor microbiota is able to influence the tumor-promoting inflammatory activity. This process exerts by a decrease of the cell proliferation activity or by a conversion of the tolerogenic TME to an immunogenic activity [17,18,21,34,140]. Novel studies seem to suggest that the systemic administration of antibiotics is able to determine the decrease of the immune checkpoint blockade efficacy and consequently aggravate patient survival [13,140,141]. In the specific case of hematologic cancers, recent preclinical studies suggest an accurate balance, while antibiotics or gut bacterial translocation are able to induce, in genetically-predisposed subjects, the leukemia development and the malignancy progression [19,136,142] (Table 6).

Prebiotics and Probiotics

In the clinical practice, targeting gut microbes is complicated by several factors such as antibiotic preconditioning, administration protocol, frequency of modulation, and dietary recommendations [138,143,144] (Table 7). Prebiotics, post-biotics, and dietary schedule oriented to the conditioning of the gut microbiota seem to represent promising procedures in the oncology practice. Many different dietary protocols have been studied recently, evidencing several epidemiological correlations but few causal mechanisms [139]. The emerging difficulties concerning the dietary data reporting is able to contrast emerging evidence and strong findings, although metabolomic data that can show dietary intake and concomitant small-molecule effectors could represent a determinant tool for this purpose (Table 7). Prebiotics, including starch, inulin, and mucin, are molecules that are able to promote the proliferation and the growth of beneficial bacteria species. These molecules showed promising findings in several preclinical models, through the improvement of the anti-neoplasm immunity and the oncological therapy response against melanoma and colon tumor. Today, experimental findings concerning postbiotic molecules is limited in clinical oncology, they may provide advantages through defined composition and manufacturing reproducibility [145,146]. Gut microbiota could also be modulated in neoplasms by fecal microbiota transplantation, the administration of specific microbial species and commercially-available probiotics. The fecal microbiota transplantation reported to be highly effective against *C. difficile* colitis, and also moderately for the immunotherapy-related colitis therapy [143,147,148]. The long-term effectiveness and stability of fecal microbiota transplantation is presently still unknown [149]. Recent clinical studies reported that fecal microbiota transplantation obtained from donors responsive to immunotherapy are able to increase the antitumor immune and clinical response to the theraphy [143,144]. More recent CTs are investigating the clinical effectiveness of microbial transplantation, through different level of consortia complexity varying from monoclonal microbe strains to multiplexed bacterial species. A limited range of commercial probiotics has been assessed considering the anti-neoplastic and systemic immunity impact, while some probiotic formulations are correlated to a tumorigenesis increasing [150]. In critically health-compromised subjects, the commercial probiotic administration could even produce a bacteremia [151]. That is why non-discriminate commercial probiotics administration in subjects affected by tumors should be discouraged. More clinical trials concerning the microbiome modulation assessment are additionally crucial for their success in clinical use and for ameliorating the oncology theraphy protocols. These protocols take advantage from the gut microbiota modulation by transplanted fecal microbioma applyied in refractory cancer demostrating clinical efficacy and positive immunity changes in the gut and tumor environment [152] (Table 7).

Bacteria Therapy

In literature, the efficacy of some microbial species can produce important contribution to cancer tolerogenic programming [149], other intratumoral microbes and antigens are able to induce a strong immunostimulatory action. In this way, cancer treatment with bacterial have origin in an ancient clinical practice that has been reported in documents of 1550 B.C. collected in the Ebers Papyrus [153,154] and attributed to Imhotep (~2600 BCE), an Egyptian physician. The author suggested a crude therapy for tumors and swelling through the administration of a cataplasm applied at the level of the site followed by an incision, producing an infection. In ~1200 A.C., Laziosi reported a spontaneous regression of a septic and locally ulcerative tibial bone malignancy elected for a full amputation procedure [153,154]. The accreditation of the germ theory sustaining the infectious illnesses, in 1800 Busch and Fehleisen independently described that *S. pyogenes* septic infections were correlated with spontaneous cancer regressions in a wide pool of subjects [154]. Coley reported an assessment of a highly controversial and lethal live vaccine or heat-killed *Streptococcus* and *Serratia spss.* on terminal subjects [154,155]. The author reported a >10-year disease-free survival in 60 subjects (30%), demonstrating the first clinical application of immunotherapy protocol in history [23]. Recently, the recent advances in molecular biotechnologies and protocols, the high quantity of naïve-bacteria species delivery and the engineering protocols are commonly available in order to produce innovative neoplasm adjuvants therapy [73]. Moreover, the microbes therapy against high-risk cancer, non-muscle invasive bladder neoplasms through live-attenuated *M. bovis* has been ap-

proved by the FDA [156]. In this way, a wide spectrum of microbe compounds, protocols, strategies are constantly under literature assessment, research and development. The microbes could be effectively delivered through an intratumoral or intravenous administration, that could produce more than ~10,000-fold accumulation in neoplasms compared to liver, spleen and lung organs [157–159] (Table 8).

Corynebacterium Parvum: An Immunomodulator against Cancer

At the end of the last century, an impulse to the immunology procedure was proposed as a novel source against cancer through the administration of living/killed microbes. For many decades, the most investigated microbes for this purpose were the Calmette-Guérin bacillus (attenuated *M. bovis* line, and *C. parvum*) administered through percutaneous delivery or intratumorally. In this study, the CGB demonstrated to produce the neoplasm lysis and delay/arrest of the neoplasm growth via innate immunity activity [160–164]. The Calmette-Guérin bacillus is currently the standard treatment for subjects with a non-muscle-invasive bladder neoplasm through mucosal infiltration, besides as anti-tuberculosis vaccination vector [160]. *Cutibacterium acnes* has been deeply studied concerning its effect on skin microbiome. In 20th century, the microbe was known as *B. acnes*, and re-classified as *Corynebacterium*, while it is characterized by an anaerobic metabolism and properties adherent to propionic acid microbes. Due to these considerations, the nomenclature has been maintained as *P. acnes* till 2016, while it was reconsidered as *C. acnes* in relation to the genomic adaptive characteristics. This microbe is a Gram-positive anaerobic bacillus that is a physiological component of the skin microbiome. *P. acnes* is characterized by an immunomodulatory action when administered in heat- or phenol-killed suspension. It is able to induce the macrophage function, oncolytic features and it could represent a considerable adjuvant effect when combined with normal vaccines-enhancing soluble and cell-mediated immune response. The main mechanisms associated to the *P. acnes* modulation effectiveness on innate and acquired immunity are modulated by interferon and several pro-inflammatory cytokines and correlated to TLR2, TLR9 and MyD88. The microbe has been primarily registered as an adjuvant and immunomodulator, and to date, *C. parvum* has been combined with chemotherapy for the treatment of colon tumors through multiple Coparvax preparation injection. Study cohorts reported positive findings concerning the safety and life quality, but reported no significant effectiveness concerning the overall survival rate. The intrapleural and intraperitoneal administration in peritoneal malignant carcinosis resulted to be effective also for cancerous exudate decrease and pleurodesis [165] . A 3 mg heat-killed *Propionibacterium acnes* intratumoral infiltration in subcutaneous melanoma is able to induce a local and systemic Th1 and Tc1 response correlated with *in situ* granuloma and cancer regression [161,166,167]. For this purpose, the administration of natural bacteria could represent a useful strategy due to their tropism for tumors. For example, some specific lines of obligate anaerobes and facultative anaerobes could colonize the hypoxic and the necrotic region inside the solid cancer mass after the systemic protocol administration [168]. The oxygen concentration at the level of the cancer mass is often strongly decreased compared to the normal healthy tissues [169]. Other studies reported that more than 10,000-fold of *S. typhimurium* could be accumulated in cancer masses compared to the other organs at 1 week from the systemic administration [166,168,169]. Bacteria that colonize a solid neoplasm mass induce a hypoxic necrosis of the cancer core due to different local mechanisms and chemotaxis. The hypoxic cancer microenvironment and the nutrients released by the necrotic neoplasm tissues and cells could improve the proliferation of anaerobic microbes. The immunosuppressive TME is able to prevent the immune system response against the tumor bacteria especially during the early stage. In this way, these bacteria colonies activate the host's immune system, producing chemotaxis and the infiltration of a wide number of immune cells within tumors [169,170]. On the other hand, the listeria species have been reported to potentially infect the bone marrow-derived suppressor cells (MD-SCs) at the level of the cancer site, inducing a consistent decrease of bone marrow-derived suppressor cells and subsequently transforming the immuno-suppressive environment to an immunostimulatory activity [171]. *C. Bacillus* lines are able to destroy neoplastic cells due to exotoxin secretion. In fact, some modulators, hemolysins and phospholipases are able to kill cancer cells acting on the membrane components. Clostridium strains are able to activate neoplasm apoptosis by a trigger on the release of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from neutrophils cells. The early proliferation of the Clostridium strains in solid neoplasms can produce an intratumoral infiltration of granulocyte and macrophage cells, when the increased release of chemokines is able to produce a significant triggering on the adaptive immunity and provide the immune cells chetaxis to the neoplasm site [159]. The Salmonella is a microbe strain that has been investigated as a key source for anticancer therapy. The Salmonella interaction with the host immunity and mechanisms of action have been well clarified in the recent literature [159]. After the cancer infection, the Salmonella is able to directly kill the tumor cells through activating the autophagy path or inducing apoptosis [172]. A recent phase I study, an attenuated *S. Typhimurium* line was used on a total of 24 subjects affected by metastatic melanoma and on 1 patient affected by metastatic renal carcinoma [169,173]. The study findings reported no tumor regression at the follow-up. The study data reported that additional techniques are necessary to achieve an improvement of the treatment effectiveness and to reduce the toxicity. Therefore, although na-

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tive anaerobic and facultative anaerobic microbes revealed higher propension to form active colonies in cancers and killing neoplastic cells by infiltration of immunity cells, the single functionality and non-effective therapy activity could mainly limit the colonies development and clinical using. On the other hand, evidence of toxic and side effects after systemic administration of native microbes was reported [173]. Due to the recent advances and insights in biotechnology, microbes could be successfully engineered to provide a safe clinical application with an attenuation protocol [174–176]. Some strains are genetically attenuated, auxotrophic, and inducible cell lines of *Escherichia*, *Bifidobacterium*, *Listeria*, *Shigella*, *Clostridium*, *Lactococcus*, *Vibrio*, and *Salmonella* have been subjected to engineering protocols. These strains reported an interesting anticancer effectiveness in several preclinical models with intravenous administration, intratumor infiltration and oral prescription [156]. These microbes have also been investigated as intratumor reactors that could induce the remodulation in the extracellular environment. Another useful technique is able to increase the engineered microbe lysis, that is able to activate the anti-cancer protein induction and local release in case of determined bacteria population density [177–179]. This model is able to reduce the size of the bacterial colonies and potentially prevent side effects correlated to a systemic toxic induction. Din *et al*. [172] reported that non-pathogenic *E. coli* and *Salmonella* are able to be subjected to engineering processes in order to achieve the lysis at a predetermined colony density, inducing the extracellular release of a chemokine, modulators, hemolysin, and/or pro-apoptosis molecules, into the TME at defined periodic intervals. These mediators are released cyclically as the bacteria colony is programmed to produce a cycle of growth-death-regrowth. Another study investigated the same mechanism of action for the inducing and releasing of antiCD47-fragment nanobody, in order to produce a DC phagocytosis inhibition [180]. This model is able to induce a tumor antigen–specific CD8+ T cell activity in order to prevent cancer metastasis and modulate an abscopal evidence, able to produce a mass regression also in distal non-injected cancers. Gurbatri *et al*. [175] investigated and engineered *E. coli* strain through transforming the PD-L1 and CTLA-4 sequences in order to provide a safe and locally controllable expression of the nanobodies antagonists. Other PAMPs, including the flagellin, could be applied in form of adjuvant. The rationale is based on the capability of DCs and non-intrinsic immune cell induction [82]. For this purpose, the intratumoral flagellin administration is reported to decrease the MDSCs levels in the cancer mass. In TME, tumor-associated M2-like macrophages are able to induce the promotion of tumor growth through the inhibition of DCs maturation, MHC expression down-regulation and the T-cells chemotaxis [175].

Zheng *et al*. [152] highlighted that an engineered attenuated *S. typhimurium* strain is able to successfully suppress the cancer growth and neoplasm metastasis in murine model colon and melanoma by the secretion of FlaB.

The recent breakthrough in biotechnologies has been proposed for microbe engineering to induce the release of STING agonists after the tumor mass colonization process. Recently, Leventhal *et al*. [177] investigated an engineered *E. coli* strain to induce the expression of STING-agonist CDA in two different cancer models in mice. The *E. coli* strain was reported as an efficient trigger for anti-cancer immunity and immunological response [176]. Loeffler *et al*. [181] tested a *S. typhimurium* engineered and attenuated strain in order to overexpress LIGHT cytokines recognized as efficient molecules with anti-cancer activity. In many different mice cancer study models, the authors reported an efficient cancer suppression with no significant toxic side effects [181]. The same authors investigated an attenuated strain of *S. typhimurium* able to release the IL-18, a cytokine connected with the proliferation and activation of immunity cells [181]. In different preclinical mice tumor models, release of IL-18 is able to sensibly potentiate the anti-cancer activity of the *S. typhimurium* strain [170,182]. Light-inducing bacterial growth and photosynthesis is potentially able to influence the cancer mass hypoxia for improved immunogenicity PDT [183]. A study investigated the findings regarding an engineered photosynthetic *Synechococcus* strain due to the integration of photosensitized-encapsulated nanoparticles at the level of the bacteria surface through amide bindings, factors able to improve the intrinsic target capability of the bacteria strain [136]. The *Synechococcus* irradiated by a 660 nm laser source is able to release oxygen through photosynthetic processes and improve the cancer mass hypoxia, engaged with an increased ROS production. The photosynthesis-boosted PDT is able to suppress the primary cancer mass growth, eradicate metastatic cancer mass and it is able to prevent the lesion recurrence through reversing the immunosuppressive TME to an immune-responsive status also in triple-negative breast neoplasms in mice preclinical model. On other hands, PDT is also correlated to an anti-cancer immune response through the immunity cell apoptosis by the calreticulin up-regulation at the level of the cell surface region [184]. Photosynthesis-boosted immunogenic PDT reported to produce a consistent increase of immunity cells included CD8+ T, CD4+ T, and natural killer (NK). The process is able to induce the decrease in quantity of the immunosuppressive cells including Tregs, MDSCs, and M2-like tumor-associated macrophages (TAM) that are key factors able to suppress the anti-cancer immunity [185]. Studies integrated pDA at the anaerobe Salmonella strain surface in order to obtain the hypoxic tumor targeting combined with the photothermal pDA capability. The application of the PTT combined with bio-therapy protocols is able to produce an effective cancer mass suppression and consequently improve the therapeutic findings due to the release of TNF-α and IL-4 acting through the cell immunity and

humoral response [186]. In a recent study, researchers investigated the immune checkpoint blockade combined with photothermal functional bacteria in order to induce a triple protocol AUNP-12. This procedure reported an effective antagonism on PD-1 through a subcutaneous injection with a safe toxicological evidence [187]. The same authors applied a subcutaneous AUNP-12-loaded-PPSG administration protocol in the mass proximity to obtain a long-term antagonist local release [188]. While there are promising findings concerning phototherapy with the bacteria-based therapy, the major issues seem to be correlated to the insufficient depth of the light penetration associated to the theoretical phototoxicity produced in the skin. This aspect needs to be investigated with future trials.

The OMVs are generally characterized by cell components composed by the periplasm and the outer membrane. These components include membrane lipids, proteins, LPS, PG and other virulence components. The outer-membrane vescicles are able to interact with host PRRs to produce an innate immune response Kim *et al*. [120] investigated in *E. coli* with no *msbB* gene encoding endotoxin reporting that OMVs applied in mice colon tumor are able to induce a significant inhibition of the cancer mass growth.

Chen *et al*. [183] investigated an innovative medicine composed of DSPE-PEG-RGD-hybridized bacterial OMVs micelles coating for immunotherapy and metastatic cancer prevention. OMVs micelles that were reported to regulate the chemotherapy efficiency and the immunity modulation. This process was determined by the sensibilization of the cancer cells to CTLs through the inhibition of pulmonary metastatic melanoma [126].

A recent study by Chen *et al*. [183] investigated a hybrid eukaryotic-prokaryotic nanomedicine obtained combining the melanoma cytoplasmatic membrane vesicles combined with attenuated Salmonella strain outer-membrane vescicles.

Patel *et al*. [184] proposed an innovative bacterial-based membrane-coated nanoparticle characterized by a PC7A/CpG polyplex core coated with maleimide groups-modified bacterial membrane. The bacteria-based nanoparticles were used for an *in-situ* vaccine administration associated with radiation therapy [184]. These studies confirmed that outer-membrane vescicles are characterized by an improved permeability and retention properties, inducing an improved chemotaxis of the immunity cells to the tumor mass. Another study reported pathogen mimicking nanopathogens (NPNs) containing PAMPs by cloaking NPs with outer-membrane vescicles, that have been known by PRRs on neutrophils [125].

Bacteria-Based Toxins

In relation to the increased antigen-expression at the level of the cancer cell membrane surface, some bacterial toxins could be specifically targeted against these molecules. Some examples of this action could involve *Diphtheria*, *C. perfringens* and *Pseudomonas* toxins against cancer cells. Bacterial toxins have been demonstrated to be useful tools for tumor cell apoptosis and anti-cancer immunity activity [143]. The *Diphtheria* toxin has been investigated for anticancer protocols in preclinical and clinical studies in relation to the anti-cancer disabling effect, correlated to a high cytotoxic evidence and/or the induced anticancer immunity activation. Buzzi *et al*. [185] investigated CRM197 as treatment in a group of cancer patients. CRM197 is a nontoxic mutant *Diphtheria* toxin that presents similar immunological characteristics to the *Diphtheria* toxin [185]. CRM197 targets the HB-EGF, that is generally overexpressed by cancer cells. The same authors reported thatCRM197 subcutaneous administration is able to produce inflammatory and immunological reactions, through a biological anti-cancer response [189]. In hematologic malignancies, the fusion proteins, bacterial toxins and immunotoxins antibodies demonstrated a strong cytotoxic due to the blocking protein translation [190]. ONTAK is a fusion protein obtained by *Diphtheria* toxin and anti-IL-2 was investigated as a potential chronic-lymphocytic leukemia treatment [124]. ONTAK showed a significant overexpression of high-affinity IL-2 receptors on chronic-lymphocytic leukemia cells with a significant efficacy on this cancer line [124,132]. A repeated immunotoxin administration is necessary at the optimal dosage concentration. On the other hand, the retreatment is generally limited to the immunogenetic properties and the capability to form anti-drug antibodies.

After the procedure, many subjects produce a rapid immunity response and the consequent production of anti-drug antibodies, that could neutralize the immunotoxin activity and prohibit further local administrations. Other studies investigated the immunotoxin/bacterial toxins and chemo drugs combination as a useful tool to avoid the recognition by the host immunity system. On the other hand, the depletion of the T-lymphocytes through immunotoxins is able to be applied for immunotherapy also for other solid cancers types, due to their capability of being effective modulators for tumor immune tolerance. This technique works by the replacement of the bacterial toxins physiological binding domain with Treg receptor ligands. The Foxp3 over-expression in Tregs is able to induce an increased level of CD25 on the Tregs surface, due to the high affinity with IL-2 receptors. Recent investigations reported that the over-expression of CD25 is able to consume IL-2 in the micro-environment, where the cytokine depletion is able to induce the activated T cell apoptosis [191].

Cheung *et al*. [192] investigated a novel generation of *Diphtheria* toxin specific for IL-2 receptor, as an effective anti-tumor target able to reduce the Treg receptors. This *Diphtheria* fusion toxin reported a significantly synergical effectiveness combined with anti-PD-1 in melanoma cancer model [193].

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Spores

Many studies have investigated the intra-tumoral administration of *C. histolyticum* spores reporting the efficacy of cancer suppression in transplanted sarcomas in mice model with no significant evidence of systemic toxic adverse effects [194].

C. novyi is already known in literature for its oxygen sensitivity and mobility through the peritrichous flagella. Both of these properties have been investigated for the cancer enrichment protocol with very limited evidence of in-site spore germination. In relation to the toxic adverse effect, the *C. novyi* α-toxin gene has been removed, due to the creation of a novel attenuated *C. novyi*-NT characterized by a decreased systemic toxicity [194].

Agrawal *et al*. [168] reported that the *C. novyi*-NT spores systemic administration in mice is able to produce a cancer regression with long-term effectiveness. The anaerobic characteristic is able to determine the capability to produce a spore germination at the level of the cancer necrotic core. The germinated bacteria are able to induce apoptosis in the pheriperal region of the cancer through the local secretion of lipases, proteases and enzymes. The host tissues are able to respond locally and to release cytokines including IL-6, MIP-2, G-CSF and TIMP-1, able to induce intratumoral chemotaxis of different immunity cells. The study also reported that 30% mice affected by cancer have been cured with significant efficacy. In a more recent study, *C. novyi*-NT spores intratumoral infiltration in dogs was able to produce an intense immunity response [194]. Moreover, Heap *et al*. [193] tested engineered *Clostridial* Spores in a mice model reporting an effective evidence of cancer mass suppression in colon carcinoma. The application of spores for anticancer purposes is currently the subject of literature investigations in human trials.

Conclusions

Recent insights in cancer and neoplasm treatment currently include a wide variety of innovative approaches that take advance from potential benefits determined by the key role played by bacteria and microbiome for the development, sustaining of the tumor microenvironment and the prognosis of the lesions. Further ongoing studies and clinical trials could provide novel inputs for innovative targeted therapies.

Availability of Data and Materials

All experimental data to support the findings of this study are available contacting the corresponding author upon request.

Author Contributions

Conceptualization, MC, MV, AS, BP, SAG; methodology, MC, AS, FL, SRT; software, FL, AS; validation, MC, MV, BP, MSDC, FL, SAG, FI, AS, SRT; formal analysis, AS; investigation, MC, MV, BP, FL, AS; writing—original draft preparation, MC, MV, BP, AS, FL; writing—review and editing, MC, MV, BP, AS, FL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.23812/j.biol.regul.homeost.agents.20233707.340.

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