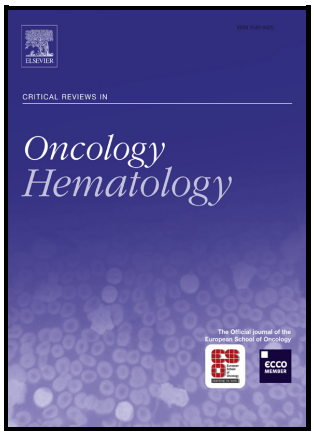

Gut and local microbiota in patients with cancer: increasing evidence and potential clinical applications

Anna Amela Valsecchi, Giorgia Ferrari, Chiara Paratore, Rossana Dionisio, Francesca Vignani, Paola Sperone, Giorgio Vellani, Silvia Novello, Massimo Di Maio

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Gut and local microbiota in patients with cancer: increasing evidence and potential clinical applications.

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Abstract

In recent years, cancer research has highlighted the role of disrupted microbiota in carcinogenesis and cancer recurrence. However, microbiota may also interfere with drug metabolism, influencing the efficacy of cancer drugs, especially immunotherapy, and modulating the onset of adverse events. Intestinal micro-organisms can be altered by external factors, such as use of antibiotics, proton pump inhibitors treatment, lifestyle and the use of prebiotics or probiotics.

The aim of our review is to provide a picture of the current evidence about preclinical and clinical data of the role of gut and local microbiota in malignancies and its potential clinical role in cancer treatments.

Standardization of microbiota sequencing approaches and its modulating strategies within prospective clinical trials could be intriguing for two aims: first, to provide novel potential biomarkers both for early cancer detection and for therapeutic effectiveness; second, to propose personalized and "microbiota-tailored" treatment strategies.

Keywords

Microbiota; Immunotherapy; Immune checkpoint inhibitors; Cancers; Biomarker.

1. Introduction

Recently, the relationship between cancer, microbiota, and oncologic treatments, especially immunotherapy, has raised the interest of the scientific community.

Several data suggest that cancer development is closely related to the disruption of the biological balance between the immune system and the gut flora community. Gut microbiota regulates epithelial mucosa homeostasis, host immunity and physiological metabolism, and dysbiosis is involved in the development of many diseases, including neoplasms [1]. Microorganisms in the local tumor environment can contribute to the onset of cancer, challenging the traditional belief that some organs are sterile.

Microbiota also play an active role in cancer cell proliferation and epithelial-mesenchymal transition (EMT), mediating the processes of carcinogenesis and recurrence. Cancer cells could acquire the ability of immunoediting, which leads to bypass the immunosurveillance and escape the physiological immune mechanism of preventing uncontrolled proliferation and metastasis [2]. The intestinal microbes could also influence the outcome of cancer treatments, either by modifying the clinical efficacy of treatments or by favoring the development of adverse events (AEs), due to their interaction with the host's immune system, modulation of host inflammation and immune microenvironment and alteration of drug metabolism [1, 3].

Several factors can alter microbiota, modulate the tumor microenvironment, and influence the effectiveness of therapies. Cancer therapies may modulate microbiota, either by inducing dysbiosis or by affecting inflammation, local and systemic immune response. Immune checkpoints inhibitors (ICIs) target crucial pathways that regulate the immune response, preventing the autoimmunity. However, ICIs clinical effectiveness is highly variable across different cancer types and even across different patients within the same setting [4].

Several biomarkers have been investigated to predict response to ICIs: high tumor mutational burden (TMB), microsatellite instability (MSI), high expression of PD-L1, and high tumor inflammatory state. Novel studies could determine which microbial species and critical concentrations may improve the outcome of cancer therapy to help clinicians promoting an increasingly personalized approach to therapy [5]. Recent studies investigated the role of fecal microbiome transplant (FMT), with the aim of modulating the composition and diversity of gut microbiome in patients with refractory cancers, to improve ICIs efficacy [6].

There are some external factors that can differently modulate the microbiota, such as use of antibiotics, proton pump inhibitors treatment (PPI), lifestyle, or the use of prebiotics/probiotics (Fig. 1). The administration of antibiotics within the two-three months before or after the initiation of immunotherapy is associated with decreased survival rates and shortened progression-free survival (PFS), due to loss of microbiota homeostasis, effects on host tissues, and enhanced activity of resistant microorganisms [7]. PPI treatment leads to significantly worse outcomes in patients with advanced cancer, treated by ICIs, due to the interference with microbiota's diversity [8]. Patients' lifestyle may have an important impact on gut microbiota, by modulating the levels of metabolic and inflammatory biomarkers, the expression of PD-L1, and the types of commensal microorganisms. The use of prebiotics/probiotics, could be able to mediate the immune response by regulating the expression of cytokines and interleukins, affecting both clinical outcome and AEs [9].

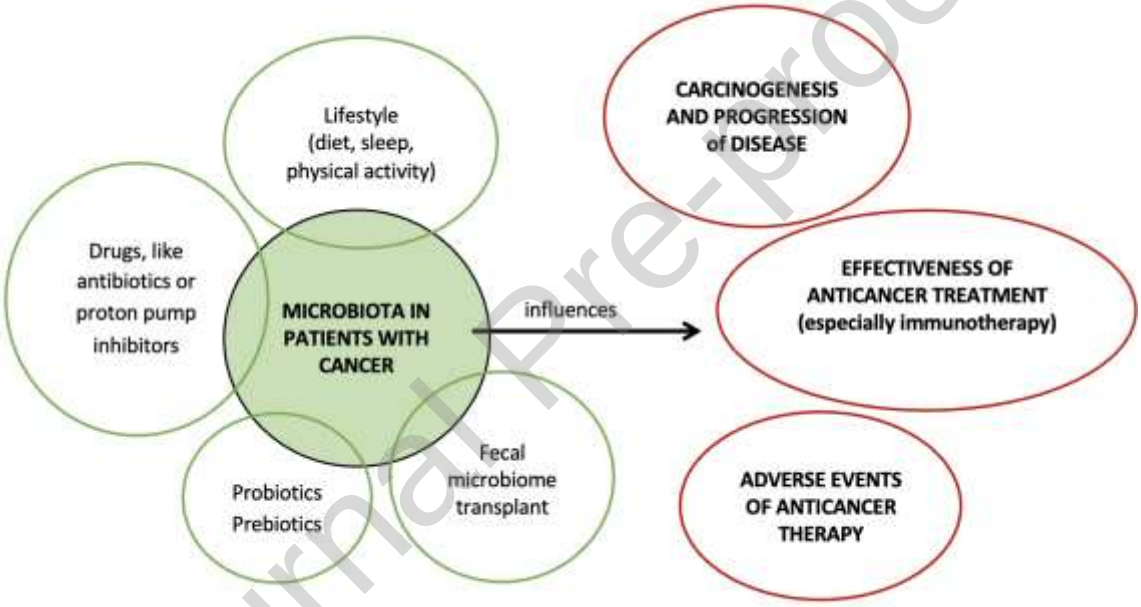

Fig. 1. The role of microbiota in patients with cancer.

In synthesis, the characterization of gut and local microbiota may lead to identify a new predictive biomarker for oncologic treatments, especially for immunotherapy, and a new target for treatment optimization.

The aims of this review are to provide a current snapshot of the state of art regarding gut and local microbiota in oncology and the most relevant studies, concluded and ongoing (Table 1. - updated to March 2023), investigating its potential clinical value in the principal tumor types.

Trial (ClinicalTrials.gov Identifier/Name of study)	Phase	Cancer type	Description	Primary endpoint
NCT04729322	II	Colorectal Cancer	Fecal Microbiota Transplant and Re-introduction of Anti-PD-1 Therapy (Pembrolizumab or Nivolumab) for the	Objective response rate

			Treatment of Metastatic Colorectal Cancer in Anti-PD-1 non-responders	
NCT04700527	I/II	Gastrointestinal, urologic or gynecologic cancer	LCCC2032: The Effects of Short Chain Fatty Acid Supplementation on the Quality of Life and Treatment-related Toxicities in Subjects Receiving Abdominopelvic Radiotherapy: A Randomized Controlled Study	Rate and severity of toxicities between subjects who receive therapeutic SCFA and those who receive placebo
NCT04988841	II	Melanoma	Assessing the Tolerance and Clinical Benefit of feCAl tranSplantation in patientS With melanOma (PICASSO)	To assess the safety of a 23-week treatment with MaaT013 combined with ipilimumab+nivolumab compared to ipilimumab+nivolumab+placebo in patients with melanoma naïve to Ipilimumab and anti-PD1
NCT03817125	Ib	Melanoma	A Multicenter Phase 1b Randomized, Placebo-controlled, Blinded Study to Evaluate the Safety, Tolerability and Efficacy of Microbiome Study Intervention Administration in Combination With Anti-PD-1 Therapy in Adult Patients With Unresectable or Metastatic Melanoma	Percentage of patients with Adverse Events
NCT03637803	I/II	Non small cell lung cancer, renal cell carcinoma, bladder cancer or melanoma	A Phase I/II Open Label, Safety and Preliminary Efficacy Study of MRx0518 In Combination with Pembrolizumab In Patients With Advanced Malignancies who Have Progressed on PD-1/PD-L1 Inhibitors	Part A: To assess the safety and tolerability of MRx0518 in combination with pembrolizumab; Part B: To assess the clinical benefit of MRx0518 in combination with pembrolizumab
NCT04139993	I	Breast cancer	A Pilot Trial of Preoperative Oral Microbiota-Based Investigational New Drug, RBX7455 to	Incidence of adverse events

			Target Immune Response in Patients with Operable Stage I-III Breast Cancer	
NCT05113485	NA	Breast cancer	A Fiber-diverse, Anti-inflammatory Diet and Aerobic Exercise Reduce Risk of Breast Cancer Recurrence	High-sensitivity C-Reactive Protein
Meet-URO 30 (SORCERER trial)	NA	Urothelial cancer	Prognostic role of gut microbiota for avelumab maintenance after first-line platinum-based treatment in patients with metastatic urothelial cancer	Comparison of gut microbial species between responders and non-responders, (population defined by progression-free survival at 4 months from the start of treatment).
NCT03341143	II	Melanoma	Phase II Feasibility Study of Fecal Microbiota Transplant (FMT) in Advanced Melanoma Patients Not Responding to PD-1 Blockade	Objective Response Rate
NCT03353402	I	Melanoma	Altering the Gut Microbiota of Melanoma Patients Who Failed Immunotherapy Using Fecal Microbiota Transplantation (FMT) From Responding Patients	Incidence of FMT-related Adverse Events; Proper implant engraftment
NCT04116775	II	Prostate cancer	A Phase II Single Arm Study of Fecal Microbiota Transplant (FMT) in Men With Metastatic Castration Resistant Prostate Cancer Whose Cancer Has Not Responded to Enzalutamide + Pembrolizumab	Anticancer effect of fecal microbiota transplant from responders to pembrolizumab to non-responders
NCT04758507	I/II	Renal cell carcinoma	Targeting Gut Microbiota to Improve Efficacy of Immune Checkpoint Inhibitors in Patients With Advanced Renal Cell Carcinoma	Number of participants who will be free from tumor progression, assessed by RECIST criteria v. 1.1.
NCT04163289	I	Renal cell carcinoma	Preventing Immune-Related Adverse Events in Renal Cell Carcinoma Patients	Occurence of immune-related colitis associated with ipilimumab/nivolumab treatment

	Treated With Combination Immunotherapy Using Fecal Microbiota Transplantation

Table 1. Most ongoing relevant studies investigating the role of microbiota in patients with cancer.
*NA: not applicable.

2. Role of gut and local microbiota in principal tumor types

2.1 Gastrointestinal cancers

Gut microbiome is affected and involved in gastrointestinal (GI) cancer development (Fig. 2). The Helicobacter pylori (HP) colonization perturbates the composition of gastric microenvironment, changing the physiological resident bacteria and the host-immune tolerance, causing abnormal modification of the epithelium [10].

Gut dysbiosis may also facilitate the progression from pre-cancerous lesions to colorectal (CRC) cancers. The prevalence of Bacteroides fragilis in the gut flora is associated to mutagenic toxins, with a potential carcinogenic effect (Fig. 2).

Gut dysbiosis may cause disruption of intestinal barrier, translocation of microbes into the bloodstream and diffuse inflammatory response, that can affect liver cells. The growth of Enterobacteriaceae and Streptococcus in gut microbiome at the expense of Akkermansia was associated to non-alcoholic fatty liver disease and hepatocellular carcinoma (HCC) [11]. The FMT from laboratory mice treated with deoxycholic acid, had a carcinogenic effect enhancing CRC growth. Similarly, FMT from CRC patients to mice promoted tumor development respect to healthy donor [12].

CRC is classically related to a lower mutational burden, an immune "cold" biology, and a low response rate to ICIs. Recently, an anti-PD1 inhibitor has been approved for the treatment of patients affected by CRC with defective gene mismatch repair and MSI-H [13]. The gut flora regulation may modulate the anti-cancer immunity and increase the efficacy of immunotherapy due to an enhanced T cell response [14]. Several data support the use of probiotics to prevent oncologic treatment AEs [9]. Administration of probiotics is associated to lower post-operative complication rate, enhanced immune modulation promoting anti-inflammatory pathway, improved tolerability to oncologic treatment and quality of life [15]. Probiotic supplementation reduces chemotherapy AEs, improve quality of life [16] and mitigate the symptoms caused by pelvic irradiation [17]. Supplement of Saccharomyces boulardii before colorectal resection had an impact on downregulation of inflammatory cytokines in patients with CRC, without increased risk of post-operative infections [18]. Peri-operative supplement of probiotics and prebiotics, such as Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus casei and Bifidobacterium bifidum, is associated to a reduced mortality and complication rates in patients with periampullary neoplasms [19].

In the last two decades, probiotics and prebiotics supplementation was focused on conventional anti-cancer treatments and related to better tolerability and enhanced effect of therapies [9, 20]. With the emerging role of immunotherapy in CRC, modulating gut microbiome with probiotic use may lead to a more susceptible immune microenvironment. The oral administration of Lactobacillus rhamnosus GG is associated to an enhanced antitumor activity of PD1 agent in a murine model of CRC, upregulating T cell immunity and tumor infiltrating dendritic cells [21]. In a mice model with CRC specimen obtained from surgical patients, the combination of IL-2 and Akkermansia muciniphila supplement enhanced the efficacy of the immunotherapeutic agent [22]. In CRC tumor-bearing mice, Lactobacillus paracasei sh2020 promoted anti-tumor immunity and efficacy of anti-PD1, enhancing CD8+ T cell activity [23].

Gut microbiome might have a role as a predictive marker for immunotherapy responses. An elevated Prevotella/Bacteroides ratio in fecal samples and the prevalence of Prevotella, Ruminococcaceae, and Lachnospiraceae in gut microbiome was associated to pattern of response to ICIs. Responders had abundance of short-chain fatty acids bacteria in fecal samples [24]. The enrichment of Akkermansia muciniphila and Ruminococcaceae spp characterized the fecal sample of patients affected by HCC obtaining a response to an anti-PD1 agent. The biological diversity of intestinal flora had progressively changed in HCC patients treated with anti-PD1 agent, distinguishing non-responders, in which Proteobacteria was predominant, to responders, where the richness of taxonomy was higher [25]. The abundance of Faecalibacterium or of Bacteroidales have been correlated to longer PFS and dismal prognosis during ICIs in HCC patients [26]. Data of microbiome in the context of immunotherapy are still at an early stage and conflicting evidence is available in literature [27].

Gut microbiota composition may be used as a predictive biomarker for CRC detection (Fig. 2). In a meta-analysis of multiple international datasets, specific microbial species were associated with CRC, (C. symbiosum, B. fragilis, F.

nucleatum, G. morbillorum, S. moorei), whereas control samples were enriched with nonpathogenic microbial species. Screening of pathogenic bacteria in oral specimen and stool samples may be a novel approach for early CRC detection [28]. Metabolic pathways correlated to high level of energy and elevated growth rates were predominant in CRC, as well as, the respective metabolite derived from microbial species: amino acids (phenylalanine, valine, leucine, alanine, isoleucine, and tyrosine) and other molecules (cadaverine, succinate, and creatine). The analysis of metabolite profiles of gut microbiome may be another noninvasive diagnostic test for CRC [28]. Some clinical trials are currently ongoing, with the aim of evaluating the impact of microbiome on anti-cancer treatments. The NCT04729322 trial has the aim of demonstrating that FMT may reverse the resistance to ICIs allowing benefit with rechallenge of pembrolizumab or nivolumab. The NCT04700527 trial has instead the purpose of assessing the toxicity of abdominal-pelvic radiotherapy with the administration of short chain fatty.

Emerging data reveals that phytomedicine may have an effect on gut microbiome regulation. Berberine, a botanical isoquinoline alkaloid, was associated to a lower β-diversity of gut microbiota in CRC mice and to a positive regulation between probiotic and pathogenic microbes, influencing Hedgehog pathway and suppressing CRC growth in mice [29]. Berberine was able to reverse dysbiotic gut microbiome in HCC, in vivo and in vitro, enhancing the level of butyric acid, a gut microbial metabolite, with a positive modulation of peroxisome proliferator-activated receptors and an inhibition on HCC development [30].

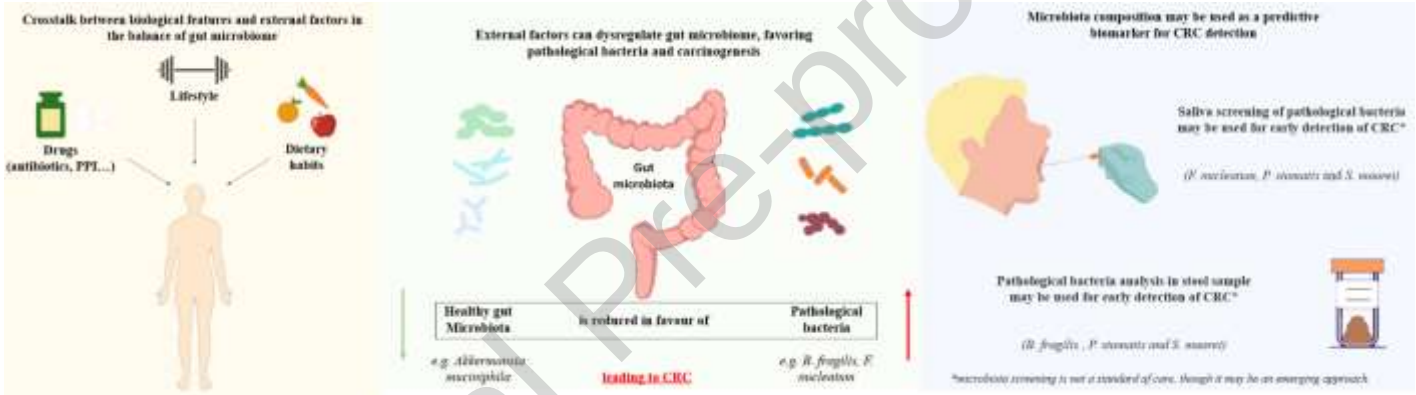

Fig. 2: Role of gut microbiota in CRC and its potential role as predictive biomarker.

2.2 Lung cancer

Dysbiosis in the lung microbiota may be associated with an increased risk of lung cancer. A positive correlation between the relative abundance of Faecalibacterium and primary tumor size [31] has been found in female never-smoker patients affected by lung cancer. Patients with epidermal growth factor receptor (EGFR) wild type non-small cell lung cancer (NSCLC) demonstrated a higher relative abundance of Bifidobacterium and Faecalibacterium and a lower relative abundance of Blautia compared to patients with EGFR-mutated NSCLC. It is uncertain whether these changes precede cancer development or follow the disease [32]. Lung cancer tends to be colonized by Gram-negative bacteria like Haemophilus influenzae, Enterobacter spp. and Escherichia coli. However, the gut microbiota of patients affected by lung cancer, when compared to healthy individuals, shows a decrease in the abundance of Firmicutes and Proteobacteria and an increase in the levels of Bacteroidetes and Fusobacteria [33].

Inflammation, bacterial infections, and other factors can prompt the gut microbiota to become pro-carcinogenic. HP has been linked to both gastric and lung cancer, with its protein toxins VacA potentially contributing to the development of cancer by inducing the production of pro-inflammatory cytokines [33].

Potentially, the composition of lung microbiota could be a valuable tool also for prognostic investigation in patients with early-stage lung cancer. The presence of Bacillus spp. in lung sputum has been linked to a higher risk of developing lung cancer [34]. Furthermore, imbalances in gut and sputum microbiota have been linked to the advancement of disease [35]. Microorganisms are known to be associated with tumor angiogenesis and metastatic processes through the regulation of vascular endothelial-derived growth factor (VEGF) expression and inflammation. Haemophilus influenzae, HPV, and HP can upregulate the expression of angiogenic mediators, chemokines, and cytokines that promote angiogenesis and inflammation in lung cancer [36]. Certain fungi, such as zj-14, zj-17, and zj-36, as well as Akkermansia muciniphila and E. hirae, have inhibitory effects on lung cancer angiogenesis. Nonetheless, further studies are necessary to fully comprehend the potential role of microorganisms in influencing the metastatic process in lung cancer.

Contrary to previous beliefs, the lung is not sterile and contains various types of microbes. The occurrence of lung cancer is linked to decreased alpha diversity (i.e. variety of microbial species in the individual), proliferation of specific bacterial taxa, and heightened bacterial density [37]. Nevertheless, there is no significant difference in beta diversity (i.e. difference of bacterial intestinal population between healthy and sick patients), between nonmalignant and tumor tissues. A study conducted on mice demonstrated that specific bacterial taxa or genera, such as Herbaspirillum and Sphingomonadaceae, exhibited greater prevalence in lung tumors compared to healthy tissue, and the augmentation of bacterial load within the lungs instigated the secretion of inflammatory molecules that facilitated cancer cells proliferation [38]. Patients with lung cancer had increased oral bacteria such as Streptococcus and Veillonella, which were associated with upregulation of MAP kinase pathway [39]. Moreover, Cyanobacteria presence in NSCLC biopsies has been linked to the production of the microcystin toxin, associated with local inflammation and lung cancer development [40].

Gut microbiota may play a role in stimulating the antitumor immune response, particularly in relation to immunotherapy. NSCLC patients who responded to nivolumab had higher gut microbiome diversity at the beginning of treatment and maintained a stable composition throughout [41]. The abundance of Akkermansia muciniphila in the gut microbiota of patients with advanced NSCLC was found to be associated with improved clinical outcomes, including response rate and survival. These finding suggested that the presence of high levels of A. muciniphila could be a potential biomarker for predicting outcomes in patients receiving PD-1 blockade. (Derosa L, Routy B, Thomas AM, et al. Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer. Nat Med. 2022;28(2):315-324. doi:10.1038/s41591-021-01655-5)

Moreover, introducing healthy donor feces in a mouse model demonstrated effective antitumor activity mediated by interferon-gamma-producing CD8 + T cells [42]. However, retrospective studies show that previous or recent antibiotic use may have a negative impact on anticancer therapy [43].

Probiotics promote lung health and reduce the severity of lung diseases by modulating the immune system through gut-lung crosstalk. Administration of Lactobacillus acidophilus during cisplatin treatment in mouse models of lung cancer has improved the anticancer efficacy of cisplatin [44]. Patients undergoing chemo-immunotherapy for end-stage lung cancer who received E. hirae and Barnesiella intestinihominis had longer PFS, indicating that the improvement in immunomodulatory effect may contribute to the increased survival [45]. Moreover, the administration of probiotic Clostridium butyricum, increasing Bifidobaterium and reducing intestinal damage, correlate with significantly longer PFS and OS in patients affected by advanced NSCLC treated with ICIs [46].

2.3 Melanoma

Alterations of gut microbiota composition may contribute to the pathogenesis and progression of melanoma [47]. The gut microbiota of patients affected by melanoma differs significantly from healthy individuals, with an increase in Saccharomytecales and Prevotella copri. A study conducted on mice has shown that intragastric administration of Lactobacillus reuteri FLRE5K1 can prevent melanoma onset, inhibit melanoma cell migration, and increase lifespan by producing anti-cancer cytokines [48]. The transfer of 11 bacterial strains, abundant in mice without ubiquitin ligase RNF5, resulted in anti-tumor immunity and limited melanoma growth in germ-free mice [49]. In contrast, the microbiota of obese mice, through the IL-6 pathway, could promote melanoma progression and lead to tumor formation after FMT in lean mice [50]. Skin microbiome may have a role in preventing and treating melanoma. A study conducted on pig models demonstrated distinctions in the bacterial diversity and composition between melanoma and normal skin, with Fusobacterium and Trueperella genera been predominant in melanoma samples [51].

Immunotherapy has revolutionized the therapeutic landscape of melanoma, but response rates are variable and is crucial to identify predictive biomarkers of ICI resistance. An altered gut microbiome is associated with poor response to PD1/PD-L1 inhibitors, while a high level of Akkermansia muciniphila was found in stool samples of respondent patients to ICIs. The oral supplementation of these bacteria or the FMT from respondent donor to germ-free mice improved the effectiveness of immunotherapy [9]. Other beneficial microbes were also identified, including B. fragilis, Bifidobacterium species, Faecalibacterium species [52], Bifidobacterium longum, Enterococcus faecium, Collinsella aerofaciens [53], and the Clostridiales family. Specifically, a high presence of Faecalibacterium spp. in fecal samples of patients with melanoma correlates with increased CD8+ T cells in tumors and peripheral blood, and reduced levels of Treg cells, pro-inflammatory cytokines and myeloid-derived suppressor cells in blood, leading to favorable clinical outcomes. Moreover, an enriched Bifidobacterium spp. microbiota is linked to a higher level of tumor infiltrating CD8+ T cells and better responses to ICIs [52].

A meta-analysis found that Faecalibacterium taxa, Ruminococcacea, and Barnesiella intestinihominis were beneficial, while Bacteroides thetaiotaomicron, Adlercreutzia equolifaciens, Bifidobacterium dentium, and an undetermined microbe from the genus Mogibacterium were associated with poor response to treatment [54].

Four studies [55-58] found that FMT, in addition to re-introduction of ICIs, is safe and promising in overcoming therapeutic resistance. Similarly to what was previously stated, responders showed higher levels of CD8+ T-cell activation and lower levels of myeloid cells. Nevertheless, the donor selection, the lack of available screening tools, and the infectious risk pose limitations to the implementation of FMT programs. The NCT04988841 trial is underway with the aim of testing the safety and efficacy of FMT in patients with melanoma. The study will evaluate nivolumab plus ipilimumab in combination with MaaT013, a standardized, high-richness, high-diversity microbiome ecosystem therapy, comparing to placebo in 60 patients.

Another focus of interest is the role of gut microbiota in the occurrence of the AEs. In a study involving 26 patients with melanoma treated with ipilimumab, high levels of the Firmicutes phylum were linked to the development of colitis [59]. Antibiotics had a detrimental effect on outcomes of ICIs in patients with melanoma, renal cell carcinoma, NSCL, and urothelial cancer [60]. However, some studies did not consider other factors that could impact the gut microbiota, such as dietary habits or other medication. The optimal time frame to avoid antibiotics before ICI therapy remains unknown, although some evidence indicates that avoiding them for at least one month before ICI therapy initiation may be advantageous [61]. Diet can also significantly impact gut microbiota and a high-fiber diet has been associated with a five-fold increase in responsiveness to anti-PD1 agents. Moreover, multiple chemotherapy agents, including dacarbazine, can lead to mutations in E. coli, in the context of resistant strains [62].

Ongoing clinical trials are currently exploring the potential benefits of combining therapeutic microbiome material and next-generation probiotics with ICIs. The NCT03817125 trial has the aim of assessing safety and potential benefits of using an orally administered microbial (SER-401) in individuals with metastatic melanoma undergoing anti-PD-1 immunotherapy. NCT03637803 is enrolling patients diagnosed with bladder cancer, melanoma, NSCLC, and renal cell carcinoma and focuses on evaluating the safety and efficacy of a proprietary bacterial strain (MRx0518) in combination with anti-PD-1 therapy. Li at al. demonstrated that concurrent use of prebiotics like mucin and inulin elicits anti-tumor immune responses and hinder melanoma growth in syngeneic mouse models [62]. Concluding, the MITRE trial is an ongoing observational study with the aim of finding biomarkers that can predict treatment response, resistance, and toxicity to immunotherapy in patients with advanced melanoma, renal cancer, and NSCLC.

2.4 Head and neck cancer

Oral microbiome has been the subject of investigations in head and neck squamous cell carcinoma (HNSCC). Several studies identified bacterial patterns linked with cancer occurrences. However, it remains unclear whether the microbiome profiles indicate the proliferation of specific bacteria in cancer microenvironment or are connected to the future development of cancer. Composition of the oral cavity differs significantly between patients diagnosed with HNSCC and healthy individuals. An increased abundance of certain commensal bacterial genera, such as Corynebacterium and Kingella, has been associated with a reduced risk of HNSCC [63]. These correlations were found to be most pronounced in current and former smokers. The study also found a potential protective effect of Actinomyces oris and Veillonella denticariosi in non-HPV carriers against pharynx and oropharynx cancer. Another study analyzed saliva specimens from treatment-naïve HNSCC cases and non-HNSCC controls, revealing variations in beta-diversity, alpha-diversity, and differentially abundant taxa [64]. They found elevated Lactobacillus species and reduced Neisseria species in murine HNSCC cases compared to controls, suggesting the potential role of microbiota profiling of saliva in detecting HNSCC.

HPV-related cancers incidence is increasing, with evidence suggesting that the virus may be a primary cause of oral cavity cancer [65]. High-risk carcinogenic HPV-16 is present in most HPV-positive oral cancers and is associated with the inactivation of tumor suppressor proteins p53, Bak, and Bax, while the E7 protein inhibits the tumor suppressor protein pRb, indicating that HPV may act as an initiating factor in carcinogenesis [66]. EBV infection is linked to a higher risk of oral and nasopharyngeal cancer (NPC), the virus is likely a contributing factor to tumor progression rather than initiation [67]. The intratissue bacterium Turicibacter has been confirmed as a diagnostic biomarker to distinguish NPC from chronic nasopharyngitis and a prognostic predictor of PFS in NPC patients [68].

Although oral fungi are an important component of the oral microbiome, they have not been extensively studied in relation to oral cancer. Nevertheless, patients with oral cancer exhibit a significant reduction in the abundance and diversity of fungal species in their oral microbiome [69]. Conversely, healthy individuals have increased levels of Malassezia fungi compared to patients with oral cancer, and the presence of Candida is negatively correlated with the presence of Malassezia [70]. Mycoplasma salivarius has been identified as the primary colonizer of oral cancer in immunodeficient individuals, but it is unclear whether its presence contributes to cancer progression or simply co-occurs with oral cancer [71].

Emerging evidence has shown an interaction between microbiota and response to immunotherapy. In the CheckMate 141 clinical trial, nivolumab significantly improved OS in patients with platinum-refractory HNSCC when compared to

investigator's choice therapy. An analysis was conducted to determine if profiling of the oral microbiome could yield prognostic biomarkers for response to anti-PD1 immunotherapy in HNSCC patients, but no significant associations were detected [72].

The oral-gut microbiota axis and the microbial-drug interaction both require more research for understanding the biological behavior and therapeutic impacts in oral cancer. Probiotics, which can balance alterations induced in both local and intestinal microbiome induced by oral cancer treatments, have been found to reduce the incidence and severity of oral mucositis [9].

2.5 Breast cancer

Growing evidence revealed variations in bacterial abundance and diversity between breast cancer (BC) tissue and adjacent healthy tissue, as well as between cancer subtypes. Proteobacteria, Actinobacteria, and Firmicutes are the most prevalent phyla in breast tissues, with Proteobacteria being more common in tumor samples and Actinobacteria being predominant in healthy adjacent tissue [73].

In patients with estrogen receptor (ER) positive BC a relatively higher abundance of Methylobacterium radiotolerance in tumor tissue has been observed compared to healthy breast tissue, whereas in invasive breast carcinoma a decrease in it [74] has been shown. The overall bacterial DNA content decreases in the tumor tissue as compared to its adjacent healthy breast tissue, with an inverse correlation with disease progression [93]. In contrast, differences in Methylobacterium radiotolerance in lymph cancer node samples compared to normal adjacent tissues has been found [75]. Normal breast tissue surrounding cancer had a higher relative abundance of Bacillus, Enterobacteriaceae, and Staphylococcus, compared to healthy controls [76]. On the contrary, another study found more similarities between tumors and adjacent normal tissues. The presence of Ralstonia, Methylobacterium, and Sphingomonas was confirmed as the most abundant genera in breast tissue [77]. A unique viral, bacterial, fungal, and parasitic breast signatures has been discovered for each BC subtype, with ER and HER2 positive BC subtypes sharing similar patterns compared to triple negative breast cancer (TNBC). Proteobacteria was found to be the most common signature in all four BC types [78].

Significant differences in fecal microbiota have been found in relation to clinical stages of BC, including differences in the absolute numbers of Bifidobacterium and Blautia, and the proportion of Faecalibacterium prausnitzii and Blautia, also according to BMI [79]. Another study demonstrated variations in gut microbiota associated with increased body fat, emphasizing the predominance of Akkermansia muciniphila in early-stage BC. Nevertheless, variations in study populations and methodologies make it difficult to draw definitive conclusions [80].

Gut bacteria can promote BC through chronic inflammation. Bacteria upregulate toll-like receptor (TLR) through pathogen-associated molecular patterns (PAMPs), which activate NF-kB and cause the release of several cytokines, leading to persistent inflammation in the tumour microenvironment.

BC is also associated with sex hormone dysregulation. The estrobolome, a subset of gut microbiota, has been shown to influence estrogen metabolism producing beta-glucuronidase enzymes that convert estrogens into their active forms and enhance their availability for resorption into the bloodstream. Certain bacterial groups such as Clostridia, Ruminococcaceae and Escherichia/Shigella produce beta-glucuronidase [81]. Bacterial beta-glucuronidase can also participate in the deconjugation of xenobiotics and/or xenoestrogens, increasing their half-life and availability [81-82].

The relationship between bacteria and the efficacy of immunotherapy is also being studied in BC. A recent study compared patients with metastatic ER+/HER2- BC who received eribulin with or without pembrolizumab and found changes in the levels of Akkermansia and Faecalibacterium after two cycles of treatment in patients receiving eribulin [83]. Moreover, microbial metabolite trimethylamine N-oxide (TMAO) has a positive correlation with the response to immunotherapy and could serve as a predictive biomarker in TNBC. The coadministration of an anti-PD1 antibody with TMAO or a choline-rich diet resulted in more significant suppression of tumor growth in vivo than the antibody alone, providing a rationale to investigate the use of TMAO or choline as an immunosensitizer to induce a response to immunotherapy in TNBC [84].

Recent in vivo and in vitro studies have explored how probiotics affect BC. Lakritz et al. conducted a study in which both a group of mice genetically engineered to develop human breast tumors and a group fed a Western-style diet were administered probiotic lactic acid microbes, revealing that the Lactobacillus reuteri probiotic inhibited early-stage carcinogenesis through an immune cell-mediated process and increased breast cell sensitivity to apoptosis [85]. Other studies conducted on mice have demonstrated that the administration of L. acidophilus, that can increase the production of IL-12 in the splenocyte culture, [86] and Lactobacillus helveticus R389, that enhance IgA and CD4+ cell levels in mammary glands [87], possess chemopreventive effects on cancer development. Japanese females exposed to L. casei Shirota, and soy isoflavones over an extended period exhibited a chemopreventive impact on cancer growth [88].

The NCT04139993 ongoing trial has the aim of evaluating the impact of a novel oral Microbiome Restoration Therapy (MRT), called RBX7455, on the immune system of patients with stage I-III breast cancer before surgery. Another ongoing trial (NTC05113485) aims to lower the risk of BC recurrence by increasing gut microbes' diversity, reducing sensitivity to C-reactive protein and visceral body fat through a combination of aerobic exercise and intake of highly-microbiota-accessible food.

2.6 Gynaecological cancers

The available data on the role of microbiome in gynaecological cancers (ovarian cancer, OC; endometrial cancer, EC; cervical cancer, CC) are very preliminary. Gynecological and gastrointestinal tract dysbiosis seems to have a role both in carcinogenesis and in neoplastic progression because of regulation of estrogens levels, modulation of inflammatory response, interference with carbohydrate metabolism, and production of toxins and metabolites [89]. In most women of childbearing potential, the vaginal and cervical microbiota contains Lactobacillus species, while the upper gynecological tract is dominated by a low-biomass microbiome with a diverse mixture of microorganisms. All pathophysiological alterations of the gut–uterus axis may spark gynecological cancers [89].

The gut microbiota of women with OC has been studied as potential biomarker of screening and early detection. In fact, OC is characterized by dysbiosis which can be found in numerous body sites (tumor tissue, upper and lower female genital tract, peritoneum, serum, intestines). Distinct group of viral, bacterial, fungal, and parasitic signatures of high significance in OC, including retroviridiae and HPV, several members of Proteobacteria and Firmicutes, yeasts, zygomycetous fungi and specific viral integration sites have been shown within the host genome of OC samples, which might be involved in carcinogenic process [90]. A unique profile of bacterial phyla (Proteobacteria, Firmicutes, Acinetobacter, and Lactococcus) has been detected in the peritoneal fluid of women with OC. Proinflammatory–microbiota interactions may potentially mediate systemic immune response during carcinogenesis with the activation of specific cytokine- and stimulus-related patterns: in particular C-reactive protein (CRP) serum levels are significantly lower and tumor necrosis factor-alpha (TNF-α) levels are significantly higher in the microbiota dysbiosis group of the study [91].

Microbiome can probably influence the response rate to drugs. In a pilot study, the microbiota of 24 women with OC was prospectively profiled and its evolution was reconstructed in relation to therapeutic response during neoadjuvant or adjuvant chemotherapy to follow-up. Gut microbiota of platinum-resistant patients was enriched in Coriobacteriaceae and Bifidobacterium (lactate producers), whereas gut microbiota of platinum-sensitive patients was enriched in the Veillonellaceae family (lactate utilizers). These microbiome signatures were detectable within the first chemotherapy cycles, suggesting that early integrated treatments could affect prognosis and clinical outcome [92].

The use of antibiotics can affect gut microbiota and anticancer drug efficacy. In OC, a study conducted on mice demonstrated that antibiotic treatment promoted tumor growth and conferred cisplatin resistance because of reduced apoptosis and increased DNA damage repair and angiogenesis [7].

2.7 Urological cancers

Microbiota may hold a crucial role both in cancer initiation and treatment response in prostate cancer (PC), renal cell carcinoma (RCC) and urothelial carcinoma (UC).

Regarding PC, estrogens play a pivotal role by determining an antiandrogenic effect inhibiting LHRH. The group of gut bacteria able to metabolize estrogens, called "estrobolome", may increase estrogens deconjugation through the secretion of β-glucuronidase, favor the binding between circulating estrogen and ERs, and stimulate cell proliferation and promote the development of PC [93].

Microbiota has a role also in disease progression: gut dysbiosis and Proteobacteria enrichment encouraged greater gut permeability and increased intratumoral lipopolysaccharide, promoting PC progression via the NF-κB-IL6-STAT3 axis in mice. Proteobacteria might act, not only as a biomarker for progressive PC, but also for docetaxel resistance [94].

Transition of PC from a setting of hormonal sensitivity to resistance is caused by various factors including the presence of gut immunostimulatory bacteria. ADT itself promotes the expansion of defined commensal microbiota capable of converting androgen precursors into active androgens, contributing to endocrine resistance. The depletion of microbiota by oral antibiotics can delay the time of castration resistance [95]. ADT can be modulated by both the immunogenic (presence of immunogenic bacteria, like Akkermansia muciniphila; stimulation of tymophoiesis) and the metabolic effect (degradation of ADT-relevant drugs; androgen producing bacteria; biosynthesis of menaquinone) of microbiota [90].

ICIs represents an important treatment for patients with RCC, so new predictive biomarkers are urgently needed. Preclinical studies demonstrated that mice with specific bacterial species (Bacteroides faecalis or Bifidobacterium) derived greater benefit from ICIs due to the maturation of intratumoral dendritic cells and the expansion of anticancer Th1 cells. Microbiome profiling in patients with RCC showed that specific immunomodulatory bacteria (Akkermansia

muciniphila, Bifidobacterium, and Faecalibacterium) were enriched in patients with better outcomes [96] and specific bacteria (Prevotella copri, Bifidobacterium adolescentis, abundance of A. muciniphila and Faecalibacterium) were over-represented in responder patients [97]. The microbiota composition can be shift both by tyrosine kinase inhibitors (TKIs) and antibiotics. TKIs taken prior to ICI and the use of antibiotics markedly affected the composition of the gut microbiota, favoring the dominance of species like Clostridium hathewayi, with an impact on ICIs effectiveness [98].
Microbiota is also involved in the modulation of AEs. Sunitinib-induced diarrhea may be correlated to the defects of the butyrate-producing bacteria and the increase in Bacteroides [99].
The urinary and bladder microbiota are more involved in the carcinogenesis process of UC than the intestinal one because of the creation of a chronically inflammatory microenvironment [100].
In patients with bladder cancer, has been found an abundance of Tremellales, Hypocreales, and Dothideales with significant differences in alpha and beta diversity compared to healthy patient. A subgroup analysis by sex and neoadjuvant chemotherapy status did not show further differences in microbiome composition. A specific microbiota composition (high diversity and low abundance of Agaricomycetes and Saccharomycetes) modulated response rate to preoperative chemotherapy, both enhancing systemic immune response through antigen presentation and modulating chemotherapeutic agents through metabolism and enzymatic degradation [101].
Another study examined microbiome of patients with UC undergoing neoadjuvant chemotherapy and showed that there was no significant difference in alpha and beta diversity by responder patients. An increased abundance of Bacteroides was associated with residual disease after a radical cystectomy regardless of type of chemotherapy [102].
The R. bromii abundance in patient with bladder cancer was associated to no response to ICI, while the presence of genus Sutterella among other bacteria indicated a better efficacy of ICI [103]. Other trials are ongoing, to value if gut microbiota can be considered a valid predictive biomarker of response to immunotherapy (Meet-URO 30, SORCERER trial). Some studies are exploring the possibility to modify patient's microbiome using FMT (NCT03341143 and NCT03353402) or supplementation of live bacterial or of probiotic to improve clinical outcome and ICI efficacy. At the same time, some ongoing trials (NCT04116775, NCT04758507 and NCT04163289) are evaluating the potential role of FMT also in reversing resistance to ICIs.

3. Conclusions

In conclusion, this work is a quick but comprehensive review of the main emerging works regarding the role of the microbiota in each type of tumor. The diversity and composition of gut and local microbiota can lead carcinogenesis and progression, playing a pivotal role in the clinical response to anticancer treatment, especially immunotherapy, and influencing the onset and severity of treatment-related AEs (Fig. 1).
A limitation is that the various molecular mechanisms of microbiota modulation are not explained in detail. This is due to different reasons. First the primary aim of the review was to encourage clinicians to pay more attention to the potential *clinical value* of microbiota in cancer as predictive biomarker (the goal of this work wasn't to focus on all specific biological mechanisms of microbiota in patients with cancer). Second, most of mode of action of microbiota are uncertain and unclear in the above-mentioned studies. Surely other translational studies with larger sample size are needed to validate and evaluate the effects of functional molecular pathways of gut microbiota in cancer and in the efficacy of novel therapeutic agents.
Therefore, the interest in microbiome-based therapeutic approaches is exponentially growing and the manipulation of microbiota in patients with cancer through several strategies has become one of the newest hot topics in cancer research. For this reason, standardization of microbiota sequencing approaches and several prospective clinical trials are the key to provide validation of a novel predictive biomarker to be used and integrated into clinical practice to offer an increasingly personalized therapy to our patients and, where possible, an early cancer detection.

CrediT authorship contribution statement

Using the CRediT author statement format, individual author contributions to the manuscript were as follows: **Anna Amela Valsecchi, Giorgia Ferrari and Chiara Paratore**: Conceptualization, Validation, Data curation, Writing – original draft, Visualization, Investigation. **Francesca Vignani, Paola Sperone and Rossana Dionisio**: Conceptualization, Validation & Review. **Silvia Novello and Giorgio Vellani**: Conceptualization, Validation, Review & editing. **Massimo Di Maio**: Conceptualization, Supervision, Data curation, Validation, Review & editing.

Declaration of Competing Interest

MDM reports honoraria from AstraZeneca, Boehringer Ingelheim, Janssen, Merck Sharp & Dohme (MSD), Novartis, Pfizer, Roche, GlaxoSmithKline, Amgen, Merck, Takeda for consultancy or participation to advisory boards and direct

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CrediT authorship contribution statement

Anna Amela Valsecchi and Giorgia Ferrari: Conceptualization, Data curation, Writing – original draft, Visualization, Investigation. Chiara Paratore: Data curation, Writing – original draft, Visualization, Investigation. Francesca Vignani, Paola Sperone and Rossana Dionisio: Validation & Review. Silvia Novello and Giorgio Vellani: Validation, Review & editing. Massimo Di Maio: Supervision, Data curation, Review & editing.

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Highlights

- Microbiota has a role both in carcinogenesis and cancer recurrence.
- Microbiota can be altered by several external factors.
- Microbiota interfere with drug efficacy and modulate the onset of side effects.
- Microbiota could be biomarker for early cancer detection and therapeutic efficacy.