Review Article

Oncogene-addicted solid tumors and microbiome—lung cancer as a main character: a narrative review

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Background and Objective: Lung cancer stands as the main cause of cancer-related deaths worldwide. With the advent of immunotherapy and the discovery of targetable oncogenic driver genes, although prognosis has changed in the last few years, survival rates remain dismal for most patients. This emphasizes the urgent need for new strategies that could enhance treatment in precision medicine. The role of the microbiota in carcinogenesis constitutes an evolving landscape of which little is known. It has been suggested these microorganisms may influence in responses, resistance, and adverse effects to cancer treatments, particularly to immune checkpoint blockers. However, evidence on the impact of microbiota composition in oncogene-addicted tumors is lacking. This review aims to provide an overview of the relationship between microbiota, daily habits, the immune system, and oncogene-addicted tumors, focusing on lung cancer.

Methods: A PubMed and Google Scholar search from 2013 to 2024 was conducted. Relevant articles were reviewed in order to guide our research and generate hypothesis of clinical applicability.

Key Content and Findings: Microbiota is recognized to participate in immune reprogramming, fostering inflammatory, immunosuppressive, or anti-tumor responses. Therefore, identifying the microbiota that impact response to treatment and modulating its composition by interventions such as dietary modifications, probiotics or antibiotics, could potentially yield better outcomes for cancer patients. Additionally, targeted therapies that modulate molecular signaling pathways may impact both immunity and microbiota. Understanding this intricate interplay could unveil new therapeutic strategies.

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Conclusions: By comprehending how microbiota may influence efficacy of targeted therapies, even though current evidence is scarce, we may generate interesting hypotheses that could improve clinical practice.

Keywords: Lung cancer; oncogene-addicted tumor; microbiome; targeted therapies

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Introduction

Background

Over the past decade, there has been a notable focus on the microbiome, driven by increasing evidence linking microbiota to the natural history of tumors and its relationship with lifestyle, carcinogenesis, and responses to cancer treatments such as immune checkpoint blockers (ICB), and the severity of immune-related adverse effect (1-3). Bacteria, viruses and fungi colonize the lower respiratory tract of patients and healthy individuals. These microorganisms are thought to play a specific role, including resistance to pathogens, activation of the immune system and uptake of nutrients (4). Dickson *et al.* described that *Prevotella*, *Veillonella* and *Streptococcus* are the main genera in lung tissue of healthy individuals, although they appeared in low quantity. Compared to the gut, lung microbiota is known to vary more over time, with a consistent spatial variation (5,6). Three factors have been described to impact the composition of lung microbiota: (I) introduction of microbiomes into the airway; (II) elimination of microbiomes from the airway; and (III) regional conditions that influence microbial growth. These conditions, influenced by environmental factors such as air pollution or cigarette smoking, are the most determinant during disease. Of note, particulate matter (PM) present in the air, derived from fossil fuel combustion and pollution, has been recently associated to increased risk of *EGFR* and *KRAS*-mutant non-small lung cancer cell (NSCLC). As a result, the association between oncogenic drivers' pathways has become more intriguing, and the possibility of an impact of environmental pollution on lung microbiota is increasingly plausible. PM-associated bacteria, mainly represented by *Actinobacteria* and *Proteobacteria*, usually appear enriched in patients with chronic pulmonary obstructive disease (COPD) exacerbations and asthma, further strengthening the link between PM and disease (7-9). Other determinants, such as seasonal variations and ambient temperature, may also alter the microbiota. For example, a study of PM in China described a predominance of *Proteobacteria*, *Bacteroidetes*, *Actinobacteria*, *Cyanobacteria*, and *Firmicutes*, attributing these findings to the presence of PM2.5, air humidity, and tropical climate of the region (10). As regards cigarette smoking, responsible for nearly 80% of this highly preventable disease (11,12), it has been described to have a strong effect on microbial composition as it contains potential respiratory pathogens, such as *Actinobacter*, *Clostridium*, *Klebsiella*, *Pseudomonas* and *Serratia.* Moreover, it appears to enhance bacterial adhesion and alter host immune response, thus leading to airway dysbiosis due to chronic inflammation (13). Overall, these findings highlight a robust connection between the lung microbiome, environmental factors, and the inflammatory changes that increase vulnerability to diseases. The growing prominence of oncogene-addicted tumors in non-smokers might be attributed to external disruptors beyond cigarette smoking. Host and environmental factors, including spatial, temporal, and compositional variations, influence the lung microbiota, thus creating a dynamic microbial system within the lungs.

Rationale and knowledge gap

It must be highlighted that although "microbiome" and "microbiota" are sometimes used interchangeably, key differences distinguish both terms. The microbiome is defined as the complete set of genomes from all microorganisms in a given environment, comprising not only the community of microorganisms but also their structural elements, metabolites, and the prevailing environmental conditions. In contrast, the microbiota refers specifically to the living microorganisms present in a defined environment, such as the microbiota found in the oral and gut regions (14). This distinction is crucial for understanding the link with the host and tumor cells, as well as for the development of potential therapeutic strategies targeting the microbiota. For example, preclinical studies in mice have shown that changes in microbiota composition after antibiotic administration

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Table 1 The search strategy summary

Items	Specification
Date of search	November 2022 to May 2024
Database and other source searched	PubMed, Google Scholar
Search terms used	"oncogene addiction", "lung cancer", "MAPK", "EGFR", "KRAS", "microbiome", "airway microbiota", "gut microbiota", "tyrosine kinase inhibitors"
Timeframe	From 2013 to May 2024
Inclusion criteria	Full-text English published articles were included
Selection process	M.G. and M.L.M. conducted the initial selection independently, and obtained consensus with the authors to include relevant information

confer resistance to ICB, a phenomenon that can be reversed after fecal microbiota transplant (FMT) or co-housing, or with the use of probiotics like *Bifidobacterium* (15,16). In humans, several large series have shown unfavorable outcomes of patients under ICB while receiving antibiotics (17-19). However, while interaction between microbiota and ICBs, as well as chemotherapeutic agents, has already been well elucidated in lung cancer and other solid tumors such as melanoma, evidence regarding tyrosine kinase inhibitors (TKIs) is lacking.

Objective

The present review aims to shed light on the link between the composition of microbiota, the immune system, oncogenic drivers and targeted therapies in lung cancer scenario. Our objective is to understand the complex interplay between microbiota composition and oncogene-addiction, in order to generate hypothesis that might enhance therapeutic outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-216/rc).

Methods

This narrative review consists of previously published articles, searched in the PubMed and Google Scholar databases. The terms used to identify relevant data included "oncogene addiction", "lung cancer", "MAPK", "EGFR", "KRAS", "microbiome", "airway microbiota", "gut microbiota", "tyrosine kinase inhibitors". Articles written in English published from 2013 to 2024 were reviewed in detail, and additional, relevant articles were included to deepen information retrieved. The search strategy is summarized in *Table 1*.

Microbiota, carcinogenesis, tumor microenvironment and immune system

The Human microbiota, described by Wang *et al.* as an "essential organ", comprises nearly 100 trillion symbiotic microorganisms (20). There is evidence suggesting that microbiota generates a state of chronic inflammation, thus predisposing to various types of cancer. The impact of microbiota on patients' responses to chemotherapy, radiotherapy, immune checkpoint blockade (ICB), and targeted therapy depends on its composition and its interactions with the host, the immune system, and the TME (21-24).

Microbiota and carcinogenesis

The role of the microbiota in carcinogenesis, response to treatments and appearance of adverse effects has been extensively studied in the last 20 years (25,26). Knippel *et al.* described that bacteria secrete toxins conducting direct DNA damage, establish an inflamed environment by the generation of metabolites, and maintain a chronic infectious state that potentiates immunosuppressive responses. This author also highlighted three hypothesis that may explain bacterial involvement in carcinogenesis: (I) the driver-passenger model, where commensal bacteria coordinate with a single group of tumorigenic bacteria to promote tumorigenesis; (II) the keystone theory that states that a single bacterium can favor the colonization of additional pro-carcinogenic bacteria thus leading to carcinogenesis; and (III) the hit-and-run model that supports the concept of a

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temporary colonization by carcinogenic bacteria that favors tumorigenesis (27,28). This inflammatory, pro-carcinogenic environment not only affects tumor initiation, promotion, invasion and metastasis, but also alters immune surveillance and responses to therapy. Pathways that converge to this tumorigenic state include secretion of immunosuppressive cytokines and chemokines, activation of oncogenic pathways such as *RAS* or *MYC*, and stimulation of mechanisms that favor proliferation and invasion, including angiogenesis and epithelial-mesenchymal transition (EMT) (29). Overall, microbial effect on tumorigenesis is a well-known mechanism established in various types of cancer. Examples of this include the link between *Helicobacter pylori* in gastric cancer, human papillomavirus (HPV) in cervical cancer, and *Streptococcus bovis* in colorectal cancer (CRC) (30,31).

Microbiota and the immune system

The relationship between the immune system and the microbiota has been on the spotlight in the last few years, mainly due to the interesting findings that link microbiota composition to efficacy and toxicity of ICB (32,33). This appears to be related to the fact that the microbiota helps to maintain immune homeostasis. Wu *et al.* reviewed the role of the microbiota on innate and adaptive immunity, highlighting its contribution on the development of antigen presenting cells (APC) and neutrophils, on the immunomodulatory role of intestinal epithelial cells, on the maturation and maintenance of $CD4^+$ and $CD8^+$ T cells, as well as on the production of cytokines and immunoglobulin A (34). Microbiota modulates immunity inducing either an immunosuppressive or an anti-tumor environment by altering neutrophil migration and function, T cell differentiation, and cytokine secretion (35). An example of this is the association between neutrophil-to-lymphocyte ratio (NLR) and microbiota. This index has been correlated with prognosis in cancer, as well as cardiovascular or inflammatory diseases (36,37). Studies have shown lower NLR has been also associated to a greater diversity of gut microbiota; certain species such as *Bacteroides eggerthii* have been linked to higher NLR and thus worse prognosis (38-40). A preclinical study by Sivan *et al.* found that mice had different anti-tumor responses depending on microbiota composition. In this study, *Bifidobacterium* was associated to augmented dendritic cell function and activation of $CD8^+$ T cell response in TME (15).

As a result, the microbiota appears to play a critical role in shaping and regulating immune responses, as well as impacting on the development of immune-mediated disorders. These interactions can help regulate composition of commensal and homeostatic microbiota, or even promote a tolerigenic immune environment that leads to carcinogenesis and various diseases (41).

Microbiota and tumor microenvironment

TME plays a key role in tumor maintenance and progression (42). Dysbiosis, defined as the "*change to the composition of resident commensal communities relative to the community found in healthy individuals*", has been associated with the appearance of multiple diseases and the induction of an immunosuppressive phenotype by stimulation of M2 macrophages, which suppress cytotoxic T cell response and promote tumor growth and metastasis (43,44). This inflammatory microenvironment, together with the secretion of microbial metabolites, stimulate angiogenesis and promotes tumor growth and progression (45). Gut microbiota has been also described to participate in immune evasion by secretion of cytokines, promotion of immunosuppressive function of myeloid derived suppressor cells (MDSC) and regulatory-T (Treg) cells, recruitment and differentiation of tumor associated macrophages (TAMs) and neutrophils, and down-regulation of $CD8^+$ T-cell infiltration (46). Furthermore, certain intratumoral microbes such as *Bifidobacterium*, have been related to CD47 targeted immunotherapy response, showing that microbiota composition might be fundamental not only for cancer progression but also for therapy response (47).

Overall, evidence has clearly sought to understand the role of microbiota in health and disease. Microbiota interacts with the immune system by modulating immune responses, and the host's immune system helps maintain microbiome homeostasis. Dysbiosis can lead to a dysregulation of this delicate balance, thus promoting inflammation, immunosuppression and carcinogenesis. This intricate network of immune cells, TME components and their relationship with the human microbiome still needs to be further explored, mainly because it can deepen our understanding on carcinogenesis and help us in developing better therapeutic strategies. *Figure 1* summarizes the impact of microbiome in TME and immune reprogramming.

Microbiota in lung cancer patients

Lung cancer is the leading cause of cancer death worldwide, according to the World Health Organization (WHO) (48).

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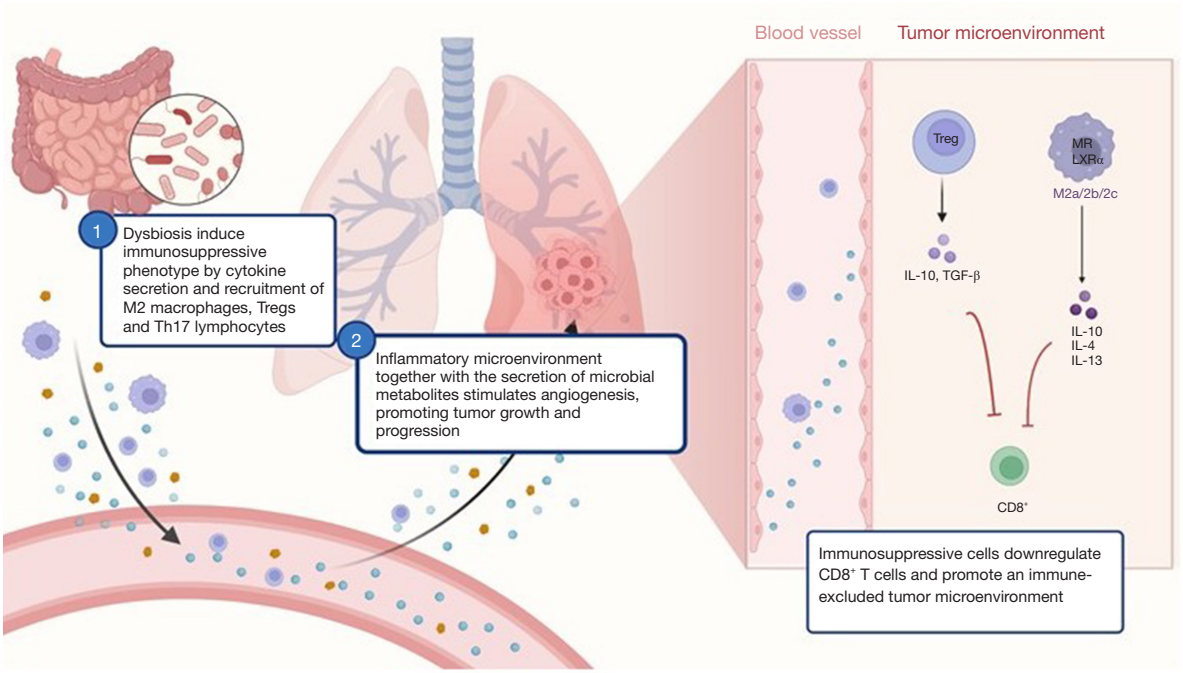

Figure 1 Dysbiosis of gut microbiota impacts lung and tumor microenvironment, conditioning immune reprogramming. MR, mineralocorticoid receptor; LXRα, liver X receptor α; Treg, regulatory T cell; IL-10, interleukin 10; TGF-β, transforming growth factor beta.

As a result, deepening our understanding of the microbiome in this subset of patients might help us comprehend disease progression and treatment response, in order to discover potential therapeutic interventions. *Figure 2* illustrates the available evidence of microbiota composition in lung cancer patients when compared to healthy subjects.

Concerning lung microbiota, Gomes *et al.* described an abundance of *Proteobacteria* in lung cancer patients, and correlated the presence of certain *Enterobacteriaceae* to worse survival. A distinct pattern was found in this study according to histology, whether adenocarcinoma, squamous cell or SCLC. An abundance of *Acinetobacter*, *Propionibacterium*, *Phenylobacterium*, *Brevundimonas* and *Staphylococcus* was found in adenocarcinoma subtype, while squamous cell carcinoma had a predominance of *Enterobacter*, *Serratia*, *Kluyvera*, *Morganella*, *Achromobacter*, *Capnocytophaga* and *Klebsiella* (49). Ramírez-Labrada *et al.* also reported several differences between healthy samples and tumor tissue, with an enrichment of *Granulicatella*, *Abiotrophia*, and *Streptococcus* in tumor tissue, and a predominance of *Bacteroidetes*, *Firmicutes*, *Prevotella*, *Veillonella*, and *Streptococcus* in healthy lungs (50). In addition, Greathouse *et al.* described an increase in diversity and richness in lung cancer samples as compared with normal tissue. An abundance of *Acidovorax* and *Klebsiella*, from phylum *Proteobacteria*, was found in smokers as well as in patients diagnosed with squamous cell carcinoma, as compared with non-smokers or adenocarcinoma subtype (51). Zhou *et al.* described an abundance of *Bacteroidetes*, *Fusobacteria*, *Cyanobacteria*, *Spirochaetes*, and *Lentisphaerae*, and lower levels of *Firmicutes* and *Verrucomicrobia* when compared to the control group (52). Similarly, other studies described an abundance of *Firmicutes* phylum in healthy lung tissue compared to controls, while associating certain families, including *Lachnospiraceae* and *Ruminococcaceae*, with reduced disease-free survival (53,54). This suggests that not only intratumoral bacteria, but also microbiota in healthy tissue, might play a role in recurrence.

Concerning intratumoral microbiota, Nejman *et al.* carried out a comprehensive analysis of 1,010 tumor samples of seven cancer types, including lung cancer, and 516 adjacent tissue normal samples. Bacteria were predominantly localized intracellularly, in cancer cells and immune cells, rising the hypothesis of whether they might play a role in carcinogenesis and tumor immunity. They also described an enrichment of *Proteobacteria* in lung cancer samples of smoker patients. This phylum was found to be associated to pathways that degrade chemicals from cigarette smoke,

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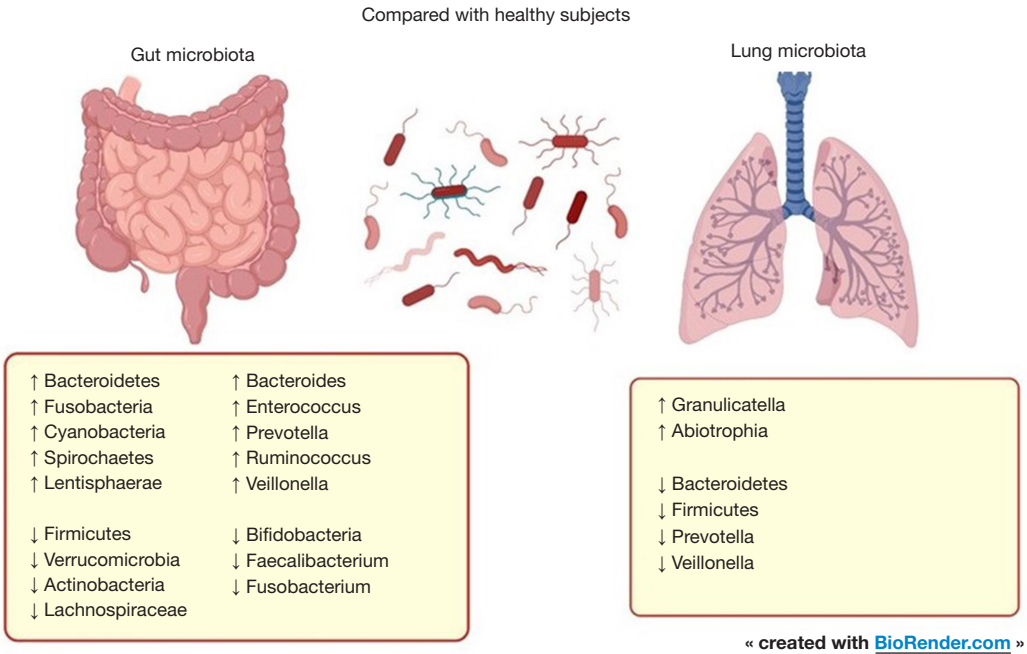

Figure 2 Gut and lung microbiota composition in lung cancer patients, as compared with healthy subjects.

suggesting that smokers may present a specific environment that induces the presence of certain bacteria (55).

Overall, the available evidence highlights the differences in microbiota composition between lung cancer samples and healthy tissue, among different histologies, and between smokers and non-smokers. It is worth highlighting that these differences raise the question on whether this variability is the cause of carcinogenesis, or if it is the result of multifactorial conditions that involve treatments used, genetic background or even lifestyle and dietary habits. This reinforces the importance of the host, the environment, and external factors in this complex interplay.

Oncogene addicted tumors and microbiota

Oncogene addiction is defined as the phenomenon of cancer cell dependence on individual oncogenes to sustain the malignant phenotype, and one of the most representative players in this setting is lung cancer (56). Oncogenic driver genes are a key element of precision medicine. Considering nearly 41% of patients with lung cancer present with stage IV at first diagnosis, it is not noteworthy that targeted therapies have improved overall survival (OS) and tolerance to oncological treatments as compared with chemotherapy (57,58). Although there is data that link targetable oncogenic drivers and microbiome, evidence is scarce. *Table 2* summarizes the current evidence.

KRAS mutation-associated microbiota

A preclinical study analyzing the impact of microbiota in *KRAS* and p53-driven lung cancer adenocarcinoma showed germ-free mice exhibited delayed tumor growth and a smaller proportion of high-grade lesions (67). However, when these mice were exposed to 14 bacterial strains cultured from late-stage lung tumors, they experienced an increase in tumor burden, thus supporting the fact that certain bacteria play a role in tumor progression. Conversely, mice with specific pathogen-free conditions that displayed at first rapid tumor growth, were administered an antibiotic cocktail of ampicillin, neomycin, metronidazole, and vancomycin, which significantly reduced tumor growth and the occurrence of high-grade lesions. This response was associated with γδ T-cells activity, which secreted IL-17A, contributing to inflammation and anti-tumor immunity. In addition, they observed higher levels of IL-22, known for its tumor-promoting effect in colorectal adenocarcinoma, and a higher expression of IFN-γ, T-bet, and CD27, which play a role in tumor differentiation and maturation. Interestingly, tumor-bearing mice had an increase in bacterial burden but reduced diversity in the airway. This reduction of diversity was accompanied by an abundance

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Table 2 Evidence of the microbiota association to oncogene drivers

Microbiome	Reference	Bacteria	Results
KRAS	Jin *et al.* (59)	*Herbaspirillum* and *Sphingomonadaceae*	Increased bacterial burden, decreased diversity. Increase in tumor burden. Treatment with antibiotics reduced tumor growth and high-grade lesions
EGFR and airway microbiome	Zheng *et al.* (60)	*Rhizopus oryzae*, *Natronolimnobius innermongolicus*, *Staphylococcus sciuri*, *Orenia marismortui*, *Burkholderia multivorans* and *Sinorhizobium*	Differences found in lung microbiome according to age, gender, smoking and *EGFR* status
	Huang *et al.* (61)	*Bacteroidetes*, *Tenericutes*, *Sharpea*, *Prevotella*, *Porphyromonas*, *Parvimonas*, *Desulfovibrio*, *Mycoplasma*, *Actinobacillus*, *Dialister*, and *Eikenella*	Alpha diversity between *EGFR* mutated and wild-type was similar. Differences in Beta diversity and in activated metabolic pathways
EGFR and Gut microbiome	Otoshi *et al.* (62)	*Blautia*	Decreased levels of *Bifidobacterium* and *Faecalibacterium* compared to controls
	Saifon *et al.* (63)	*Bacteroidetes* and *Firmicutes*	Higher alpha diversity in mutated. Similar Beta diversity between cohorts. *Actinobacteria* enrichment in patients with progressive disease after *EGFR*-TKI treatment
EGFR and intratumoral microbiome	Zhang *et al.* (64)	*Serratia marcescens*	Negative correlation to *Haemophilus parainfluenzae*. *Serratia marcescens* associated to better overall survival
MAPK pathway in other tumors	Boonanantanasarn *et al.* (65)	*Enterococcus faecalis*	Induction of *EGFR* pathway in patients with oral cancer. Production of H_2O_2 or EGF-like signals which stimulate cell proliferation
	Wong *et al.* (66)	*Helicobacter pylori*	Increase in EGF protein and *EGFR* mRNA expression in the antral mucosa to promote injury repair and ulcer healing, but increasing risk of malignancy

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; MAPK, mitogen-activated protein kinases.

of *Herbaspirillum* and *Sphingomonadaceae* in tumor samples, in contrast to the predominance of *Aggregatibacter* and *Lactobacillus* in healthy lungs (59,67). Sui *et al.* investigated the relationship of *KRAS* pathway with the intestinal microbiota in the tumor tissues of patients with CRC. The study found that the presence of *KRAS* was associated with a significant reduction in bacterial diversity and richness in the intestinal microbiota. Additionally, specific bacterial taxa such as *Roseburia*, *Parabacteroides*, *Metascardovia*, *Staphylococcus* and *Bacillales* were found to be more abundant in patients with *KRAS* mutations compared to those without (68). The expression of *KRAS* and *BRAF* have also been described to increase in the presence of *Bacteroides fragilis* and *Fusobacterium nucleatum*. Evidence highlights that these bacteria promote the development of CRC by modulating T-cell adaptive immunity and secreting cytokines (69).

Overall, these findings suggest that *KRAS* gene mutations may be associated with alterations in the intestinal microbiota, highlighting the importance of investigating the role of the microbiota in cancer development and progression.

EGFR mutation-associated airway microbiota

In 2021, a study collected 47 samples of lung microbiota obtained by bronchoalveolar lavage. Among these, there were 32 samples that were obtained from patients diagnosed of *EGFR* mutated (*EGFRm*) NSCLC. The study revealed an abundance of *Rhizopus oryzae*, *Natronolimnobius innermongolicus*, *Staphylococcus sciuri*, *Orenia marismortui*, *Burkholderia multivorans* and *Sinorhizobium* in the *EGFRm* subgroup (60). Huang *et al*. conducted another study involving 85 patients diagnosed with lung cancer, 66 of which were adenocarcinomas, with 21 being *EGFRm*. The analysis of sputum microbiota showed an enrichment

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of phylum *Bacteroidetes* and *Tenericutes*, genera *Sharpea*, *Prevotella*, *Porphyromonas*, *Parvimonas*, *Desulfovibrio*, *Mycoplasma*, *Actinobacillus*, *Dialister*, and *Eikenella* in *EGFRm* patients compared to those with wild-type *EGFR*. Subgroup analysis of non-smokers showed an abundance of phylum *Bacteroidetes* and genera *Parvimonas* and *Actinobacillus*. Differences were also observed between patients with early-stage and metastatic disease (61). It is worth mentioning that bacteria *Parvimonas*—specifically *P. micra*—has been previously associated to CRC due to its role in promoting an inflammatory microenvironment and contributing to carcinogenesis (70). *Actinobacillus* has also been described as influencing the production of inflammatory cytokines, appearing enriched in COPD, and potentially playing a role in the development of lung carcinogenesis (71). *Tenericutes* and *Bacteroidetes* have been reported to exacerbate COPD by contributing to the maintenance of a chronic inflammatory response in bronchial mucosa (72). These results highlight the association between chronic inflammation and a pro-tumorigenic role of certain bacteria present in *EGFRm* patients, leading to lung carcinogenesis independently of cigarette-smoke damage in lung epithelial tissue.

EGFR mutation-associated gut microbiota

Concerning *EGFRm*-associated gut microbiota, a study involving 37 female never-smokers diagnosed with lung adenocarcinoma investigated the relationship between cancer progression and gut microbiota, taking into consideration *EGFR* status as one of the variables (62). The analysis revealed that the presence of *EGFR* mutation, observed in 56% of the patients, did not show a statistically significant impact on gut microbiota composition. However, it is worth mentioning that *Bifidobacterium* and *Faecalibacterium* were more predominant in *EGFR* wild-type patients compared to mutated patients, whereas *Blautia* was less abundant in *EGFR* wild-type patients. Interestingly, previous studies have associated an improved response to immunotherapy with the enrichment of *Bifidobacterium*, *Faecalibacterium*, and *Akkermansia* (73). This suggests a connection between gut microbiota and treatment response, supporting the hypothesis that resistance to ICB in *EGFRm* patients might be related to microbiota composition.

Saifon *et al.* compared the gut microbiota of 13 patients with *EGFR* wild-type and 15 *EGFRm* NSCLC patients. An abundance of *Proteobacteria* was found in the *EGFR* wild-type cohort, while the mutated patients had a predominance of *Bacteroidetes* and *Firmicutes*, bacteria that have been previously associated with severe COPD and lung cancer (63,74,75). They also analyzed changes in the microbiota composition after treatment with chemotherapy in the *EGFR* wild-type group, and after TKI treatment in the *EGFRm* cohort. However, no statistically significant differences were found. Microbiota did change in response to chemotherapy, with a decrease in *Proteobacteria* and an increase in *Bacteroidetes* and *Firmicutes*. These two last phyla were mostly enriched in patients who experienced severe adverse events. Concerning response rates, *Actinobacteria* was predominant in *EGFRm* patients who exhibited progressive disease at first evaluation after treatment with a TKI. Previous evidence has associated *Actinobacteria* to breast and lung cancer, suggesting a protective role for oral cavity cancer, whereas other studies have linked its presence to increased response to anti-PD-1 therapy in NSCLC patients (76,77). These findings highlight the intricate network between specific bacteria, cancer types, TME, therapy used and immune activity, supporting a multifactorial interaction model.

A recent study assessed gut microbiota composition and ICB efficacy in patients with *EGFRm* NSCLC. Responders exhibited an enrichment of species *Bradyrhizobium guangdongense*, *Plantactinospora* sp. BC1, *Corynebacterium stationis*, and *Methanococcus vannielii*. No similarities were found with the microbiota enriched in *EGFR* wild-type responder patients, which included *Akkermansia muciniphila*, *Bifidobacterium bifidum*, or *Bifidobacterium breve*. Interestingly, the use of antibiotics was correlated with worse outcomes, suggesting a role for dysbiosis and dynamic microbiota changes in treatment efficacy (78).

EGFR mutation-associated intratumoral microbiota

When analyzing *EGFR*-associated intratumoral microbiota, Zhang et al. published interesting results that correlated *EGFR* mutation with the intratumoral presence of *Serratia marcescens* (*S. marcescens*) in patients with NSCLC (64). *S. marcescens* is known to produce prodigiosin, a secondary metabolite with cytotoxic and immunosuppressive activity that leads cells to apoptosis using the mitochondrial pathway (79). In this study, this bacterion was associated with better OS, while *Haemophilus parainfluenzae* was linked to worse prognosis. The presence of *EGFR* mutation also correlated negatively with *Haemophilus parainfluenzae*.

Overall, although there is currently insufficient evidence to establish the impact of microbiota in *EGFR*-driven NSCLC, it represents a field of active research. This might

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help us understand, in a near future, the role of microbes in the effectiveness of TKIs, the occurrence of TKI-related adverse effects, and their influence on the modulation of the oncogene-addicted TME as well as the immune system. Moreover, it has the potential to provide valuable insights of more effective treatment strategies for oncogene-addicted tumors.

MAPK pathway in other tumors and microbiome

Focusing on the microbiota and its relationship to MAPK pathway in other tumors, a study demonstrated that the presence of *Enterococcus faecalis* in the oropharynx induced activation of the *EGFR* pathway in 20 patients with oral cancer, promoting cell proliferation by the production of H_2O_2 or EGF-like signals such as TNFα (65). In the case of *Helicobacter pylori* (*H. pylori*), its presence in gastric tissue has been linked to an increase of *EGFR* gene expression in the antrum, in order to facilitate the healing of ulcers caused by this pathogen. The *EGFR* expression levels seemed to return to baseline after successful eradication of *H. pylori*. The increased *EGFR* activity induced by epithelial injury promoted cell growth, thus increasing the risk of gastric cancer (66).

A review published by Mihai *et al.* proposed a potential role of antibiotics in order to manage *EGFR* inhibitors side effects in CRC, which may eventually also impact prognosis. This is based on the association of *Fusobacterium* enrichment with poor prognosis and resistance to chemotherapy in CRC patients. Notably, doxycycline, the antibiotic of choice for managing *EGFR* inhibitor-induced skin rash, exhibits anti-*Fusobacterium* and anti-anaerobic properties, suggesting a potential benefit for CRC patients (80). Another strategy mentioned in preclinical studies is the inhibition of *EGFR* pathway by probiotics (81). This might be an interesting approach in molecularly driven *EGFR* tumors. However, evidence is lacking and definite conclusions cannot be drawn from the available studies.

Her2, another member of the *EGFR* family, has been extensively studied in breast cancer due to the impact of targeted treatments on the prognosis of patients. Her2-overexpressed breast cancer patients show less microbiota diversity, lower levels of certain *Firmicutes*—*Clostridium*, *Blautia*, *Coprococcus*, *Ruminococcus*—and higher levels of *Bacteroidetes* when compared to Her2-negative patients (82). Microbiota composition might also have an impact on treatment efficacy in this subset of patients. It has been described that diminished levels of *Lachnospiraceae*, *Turicibacteraceae*, *Bifidobacteriaceae*, and *Prevotellaceae* in gut microbiota were associated to non-responders treated with trastuzumab, an antibody targeting Her2 (83).

TKIs

Microbiota composition has been described to alter drug concentrations by several mechanisms (84). The first-pass effect, by which the drug is taken orally and is metabolized in the gastrointestinal tract, might be influenced by gut microbiota. Microbes can also induce activation of prodrugs, alter the enterohepatic recirculation by secreting β-glucuronidases or affect bile acids composition by microbial bile salt hydrolase (BSH) enzymes and microbial 7α-dehydroxylases. All of these mechanisms influence the absorption, bioavailability and efficacy of oral drugs (85). The fact that TKIs are administered orally reveals the importance of gut microbiota composition and diversity when using these agents, as they might participate in drug metabolism and absorption, influencing pharmacokinetics as well as toxicity (86).

TKI and microbiota

Osimertinib, a third generation *EGFR*-inhibitor and currently the standard of care in first-line setting for *EGFR* oncogene-addicted lung cancer, has been described to impact on gut microbiome. However, no significant differences were observed in microbiota composition when comparing the 8 NSCLC *EGFRm* patients with 21 healthy individuals, nor changes were seen when comparing pre- and post-therapeutic samples (87). As regards erlotinib, a first-generation *EGFR*-inhibitor, a preclinical study associated the presence of *Bacteroides ovatus* and *Bacteroides xylanisolvens* in lung cancer samples treated with this drug with better outcomes. This study also reported an increase in chemokines related to anti-tumor responses, such as CXCL9 and IFN-γ, and increased OS, suggesting a synergistic effect between erlotinib and the microbiota (88-91). A retrospective analysis carried out by Tinsley *et al.*, which included 168 patients diagnosed with advanced melanoma and NSCLC, showed a decrease in progression-free survival (PFS) and OS in patients who were exposed to antibiotics during TKI treatment. The TKIs administered included *BRAF* inhibitor dabrafenib, *MEK* inhibitor vemurafenib, and *EGFR* inhibitors gefitinib, afatinib and erlotinib. The postulated hypothesis was a reduction in number and diversity of microbes due to antibiotics depleting gut microbiota, although this causal

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link could not be confirmed. The study also emphasized the importance of cytochrome 3A4 inhibition by certain medications, such as macrolides or antifungals, or its induction by rifampicin, which may have altered TKIs blood concentration thus affecting treatment response (92). A recently published preclinical study focused on the impact of microbiota in gefitinib efficacy in lung adenocarcinoma. The presence of genera *Prevotellamassilia*, *Duncaniella*, *Prevotella*, *Marinilabilia*, and *Bacteroides* in mice appeared to regulate tumor growth, suggesting a potential role of these microorganisms in the antitumor efficacy of gefitinib (93).

Focusing on other tumors and their respective targeted treatments, a retrospective study was performed in 145 patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor (VEGF) TKIs. Among these patients, those who had received antibiotics covering *Bacteroides* spp.—beta-lactam antimicrobials, clindamycin, metronidazole, carbapenem—had improved PFS compared with those who received no antibiotics or antibiotics without coverage for *Bacteroides* spp. (94). Evidence supports this by demonstrating an increase in *Bacteroides* abundance in response to cytostatic agent-induced diarrhea. Administering antibiotics that reduce these bacteria might enhance both tolerance and effectiveness of TKIs, as diarrhea is a common adverse effect that leads to dose reductions. However, no statistically significant association was found between TKI dose reductions and PFS, suggesting antibiotic administration has an effect on PFS that is independent of diarrhea (95). Further evidence highlights the fact that diarrhea alters microbiota composition by reducing its richness and diversity, and favoring the abundance of species that induce intestinal damage such as *C. perfringens*, *E. coli*, *Staphylococcus*, *Bacillus*, *Enterococcus Acinetobacter*, *Streptococcus*. These species have been previously linked to irinotecan-induced dysbiosis (96,97).

Pomej *et al.* found worse outcomes in patients diagnosed with hepatocarcinoma treated with sorafenib who received antibiotics due to bacterial infections or hepatic encephalopathy. This further supports the hypothesis that changes in composition of gut microbiota due to antibiotic administration might have an impact on TKI efficacy (98).

TKI, adverse effects and impact on microbiota

A frequent adverse effect of patients under TKIs is diarrhea, which might consequently alter the intestinal environment generating dysbiosis. An example of this was seen by a decrease in microbial diversity in a preclinical study with lapatinib, an *EGFR* inhibitor used in breast cancer (99). Another study revealed that patients diagnosed with metastatic renal cell carcinoma treated with VEGF TKIs who presented diarrhea had an abundance of *Bacteroides* spp. and lower levels of *Prevotella* and *Bifidobacterium* (95). Secombe *et al.* highlighted that rash is also a recurrent adverse effect of TKIs which sometimes requires the use of antibiotics to ameliorate it, thus causing a detrimental effect on gut microbiome (100). In fact, a cohort of 102 patients with NSCLC treated with *EGFR* TKIs was studied, and results suggested antibiotic use could be a negative predictor for efficacy and toxicity of treatment, with worse PFS and an increase in incidence of dyspnea and diarrhea (101). Microbiota might also influence the appearance of adverse effects, as previously described in a study that showed that patients treated with sorafenib for hepatocellular carcinoma had a reduced incidence of hand-and-foot syndrome when an abundance of *Veillonella*, *Bacillus*, *Enterobacter*, *Faecalibacterium*, *Lachnospira*, *Dialister*, and *Anaerostipes* was evidenced in gut microbiota. In addition, a lower incidence of diarrhea was seen in patients with increased levels of *Butyricimonas* (102).

As a result, evidence supports the impact of microbiota in TKI absorption and the resulting adverse effects of these drugs, which may influence response to treatment and prognosis (103). This is of particular importance as they are orally administered drugs, so gut microbiota interacts directly with their pharmacokinetics, as has been already described for other drugs, including digoxin, L-Dopa and non-steroidal anti-inflammatory drugs (104). It is also well known the influence of diet on gut microbiome, and the effect of food intake on certain TKIs such as gefitinib, erlotinib and afatinib by increasing the absorption in 37%, 40% and 50%, respectively (103).

To sum up, the evidence that links TKIs and microbiota places special emphasis on the role of diarrhea as a frequent adverse effect of these drugs, as well as the use of antibiotics and dietary habits, which alter microbiota composition and thus impact results to therapy.

Dietary interventions and future directions

The emergence of oncogene-addicted tumors has reshaped our understanding of cancer biology, particularly in non-smokers, where these tumors play an increasingly prominent role. As we delve into the intricacies of these tumors, the role of the microbiota is gaining recognition as

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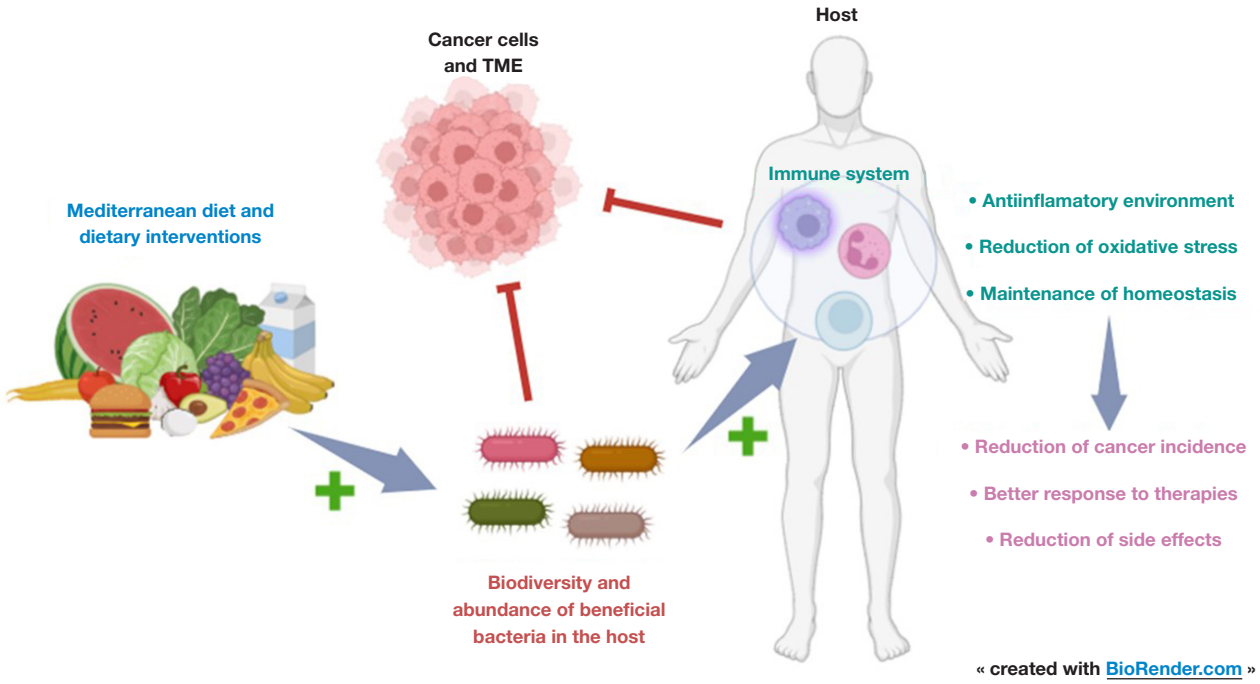

Figure 3 Interactions between dietary habits and interventions, the microbiota, the immune system, and their impact on cancer cells and the TME. TME, tumor microenvironment.

a crucial determinant. The relationship between oncogene-addicted tumors and alterations in the microbiota presents a fascinating avenue for future research. Understanding how specific oncogenic drivers interact with the microbiome, and how these interactions influence tumor behavior and treatment response, holds the potential to revolutionize targeted therapies. Exploring the dynamic interplay between oncogenic mutations, the host's microbiota, and the tumor microenvironment is poised to uncover novel therapeutic strategies. As we navigate this evolving landscape, future directions in cancer research must prioritize unraveling the intricate connections between oncogene addiction and microbiota changes, paving the way for more effective and personalized treatment approaches and lifestyle interventions.

Intervening dietary habits is an appealing approach, particularly supported by the observation that the Mediterranean diet—characterized by high dietary fiber and low processed food intake—has been associated with promoting greater biodiversity and an abundance of beneficial bacteria such as *Bacteroides*, *Lactobacilly*, *Bifidobacteria* or *Faecalibacterium*, along with a decrease in *Firmicutes* and *Proteobacteria* (105). This fosters an anti-inflammatory environment and reduces oxidative stress, maintaining homeostasis (106). *Figure 3* summarizes these interactions. Other interventions such as the use of probiotics, prebiotics, synbiotics and FMT appear to be promising strategies. Additionally, it's crucial to recognize that adverse effects of cancer treatments, such as diarrhea, and the frequent use of antibiotics in immunosuppressive patients, impact microbiome composition and reduce microbial diversity (107,108). As a result, there are many clinical trials ongoing in order to investigate the role of microbiome in response to immunotherapy and dietary interventions. However, there is a noticeable scarcity of trials focusing on oncogenic-driven lung cancer, microbiome interactions, and the impact of targeted therapies. This research gap limits our understanding of the intricate interplay among targeted therapies, lung cancer, and the microbiota (109). *Table 3* summarizes the ongoing clinical trials regarding NSCLC treatment and microbiome.

In summary, these interventions have promising therapeutic potential and represent a challenging strategy to enhance clinical response to oncological treatments with targeted therapies. Changes in microbiome due to dietary habits and lifestyle may help in this setting, as well as in reducing toxicities. Indeed, interventions for general population and environment may help to reduce cancer

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Table 3 Summary of active clinical trials of microbiome and NSCLC treatments

Clinical trial	Study title	Study type	Aims
NCT05502913	Fecal Microbiota Transplantation With Immune Checkpoint Inhibitors in Lung Cancer	Interventional, recruiting	Safety and efficacy of FMT treatment combined with first-line (chemo-)immunotherapy in metastatic lung cancer
NCT04680377	Using Microbiome to Predict Durvalumab Toxicity in Post- Concurrent Chemoradiation Therapy (CCRT) NSCLC Patients (Microdurva)	Observational, recruiting	Determine if examining the microbiome in non-small cell lung cancer participants who will receive durvalumab can predict treatment toxicity
NCT04107168	Microbiome Immunotherapy Toxicity and Response Evaluation	Observational, recruiting	Saliva and a series of stool samples will be collected from patients with melanoma, renal or lung cancer receiving checkpoint inhibitors to analyse their microbiome and will be linked to treatment response
NCT05037825	The Gut Microbiome and Immune Checkpoint Inhibitor Therapy in Solid Tumors	Observational, recruiting	Assess the associations between the gut microbiota (composition and function), host immune system, and ICI treatment efficacy across multiple cancer types
NCT04711330	Response and Toxicity Prediction by Microbiome Analysis After Concurrent Chemoradiotherapy	Observational, recruiting	The predictive value of the microbiome (throat swabs, stool and of bronchial samples) to identify patients who will relapse during durvalumab treatment after CRT (false negative rate) at 6 months
NCT03068663	Microbiota and the Lung Cancer (MICA)	Interventional, recruiting	Study the composition of the microbiota from the lung, the upper airways and the gut, in patients who undergo surgical treatment or chemotherapy. These results will serve as a base for a future study, focused on manipulation of the microbiota by prebiotics, probiotics or synbiotics
NCT05303493	Camu-Camu Prebiotic and Immune Checkpoint Inhibition in Patients With Non-small Cell Lung Cancer and Melanoma	Interventional, recruiting	Determine safety and tolerability and measure objective response rate in patients treated with checkpoint inhibitors and Camu Camu (prebiotic potential)
NCT04965129	Supplementation of n-3 PUFA in the Modulation of Lean Mass in Patients With Lung Cancer Receiving a High-protein Diet	Interventional, recruiting	The purpose of this study is to assess the effects of fish oil supplementation in the modulation of lean mass and intestinal microbiome in patients with lung cancer undergoing treatment with immunotherapy, chemotherapy and tyrosine kinase inhibitors receiving a high-protein diet
NCT04636775	Microbiome in Immunotherapy naïve NSCLC Patients Receiving PD-1/L1 Blockade (MIP_NSCLC)	Observational, recruiting	Determine if examining the microbiome in non-small cell lung cancer, immunotherapy naive participants can predict the effectiveness of immunotherapy treatment as well as determine ahead of time adverse events and their severity. In addition, the investigator will look into microbiome changing modifiers
NCT05037825	The Gut Microbiome and Immune Checkpoint Inhibitor Therapy in Solid Tumors (PARADIGM)	Observational, recruiting	Large cohort design to assess the associations between the gut microbiota, host immune system, and ICB treatment efficacy across multiple cancer types
NCT05777603	Study of Aerosolized Antibiotics and Pembrolizumab in Advanced Non-small Cell Lung Cancer	Interventional, recruiting	To test two inhaled antibiotics (aztreonam and vancomycin), combined with a standard cancer treatment, in people with NSCLC. Bacterial changes may aid in treatment efficacy
NCT05286294	Microbiota Transplant to Cancer Patients Who Have Failed Immunotherapy Using Faeces From Clinical Responders (MITRIC)	Interventional, recruiting	Phase Iia study evaluating the safety, feasibility and efficacy of FMT to cancer patients not responding to ICB therapy, using ICB-responders as donors

NSCLC, non-small cell lung cancer; ICI, immune-checkpoint inhibitor; CRT, chemo-radiotherapy; ICB, immune checkpoint blocker; FMT, fecal microbiota transplant.

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incidence, as well as side effects due to immunotherapies and targeted therapies for solid tumors. Nevertheless, there are still some uncertainties on the risks they might represent. It is more and more clear that cancer strategies require public interventions beyond oncology approaches. To better address these uncertainties, translational and preclinical research strategies are clearly needed and will provide better evidence for this scenario.

Conclusions

Oncogene-addicted lung cancer prognosis has changed dramatically since the appraisal of TKIs. Emerging evidence suggests that the microbiota may influence TKI effectiveness, due to its impact in drug absorption and metabolism. While extensive research is being conducted on the immunomodulatory role of the microbiota, as well as its impact on response to treatments and the occurrence of adverse effects, particularly with ICB, limited evidence addresses its role in targeted therapies.

Understanding the complex interaction between the microbiota, the immune system and oncogene-driven tumors could unveil prognostic and predictive biomarkers that can enhance the approach of oncogene-addicted lung cancer. New therapeutic strategies involving interventions in the microbiome, such as FMT or the use of probiotics, prebiotics, synbiotics, or changes in dietary habits, offer encouraging pathways to improve outcomes in this challenging and deadly disease. Although much has been learnt about the microbiome, the immune system, and cancer treatments in the past few years, there is still a long pathway to be unraveled.

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