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REVIEW

Is the pulmonary microbiome involved in lung cancer pathophysiology?

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Bronchopulmonary cancer represents the neoplasms associated with the highest mortality rate, despite diagnostic and therapeutic advances in recent decades. Early diagnosis is often difficult due to the paucity of symptoms or superinfections. Screening subjects at risk of developing lung cancer include clinical, bacteriological, inflammatory status, and genetic profile assessment. The personal microbiome has an essential role in the physiology of the human body. The gut-lung axis plays an essential role in carcinogenesis, being involved in various pathways. The lung microbiome can contribute to the development of lung cancer either directly by acting on tumor cells or indirectly by modulating the tumor-associated immune response. The gut microbiome can directly affect the response to immunotherapy in patients with non-small cell lung cancer.

Keywords: microbiome, lung cancer, microbiome, genetic alterations

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Introduction

Bronchopulmonary cancer is the malignancy associated with the highest mortality rate among all malignancies, despite diagnostic and therapeutic advances in recent decades. The often insidious onset, especially in the form of recurrent respiratory infections or "trailing pneumonia", contributes to delayed diagnosis and implicitly curative therapeutic measures, thus additionally contributing to the increase in mortality [1–3].

Due to the late diagnosis and the often non-specific symptomatology, these patients arrive in the emergency department as a first presentation, requiring time in Intensive Care Services before having a definite diagnosis of lung cancer. That is why, in the last decades, a particular emphasis has been placed on screening methods and the factors involved in carcinogenesis [1,3].

A new and exciting approach to lung cancer is personalized medicine that allows the individual assessment of subjects at risk for this pathology and the predictive patterns of early diagnosis [1].

Although smoking is the leading risk factor for lung cancer, there are other risk factors whose direct contribution to carcinogenesis has been demonstrated [3]. There is clear evidence of the involvement of lung inflammation and genetic mutations in the progression of the carcinogenesis process [2,3].

Lung microbiome

Initially, the scientists ignored the involvement of the lung microbiome in respiratory pathology because they considered a healthy lung sterile [4]. Invasive procedures could also explain this hypothesis by a more challenging approach to lower airways [5]. One of the first studies realized in this direction by M. Hilty in 2010 demonstrated that in the lower airways, the bacterial density is comparable to that in the upper part of the small intestine [6]. Recent studies underline that the microbiome of a healthy lung is diverse, and its modification can lead to the development and progression of various lung diseases [7].

In a healthy lung, the microbiome results from the migration of microorganisms from the upper respiratory tract or local growth under various conditions. It is characterized by *Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria,* and *Actinobacteria*. The oropharynx and upper respiratory tract flora mimic the microbiome of the lung. In contrast, the flora of the nasal mucosa is similar to that of the skin [5,8].

The human microbiota is composed of trillions of microorganisms, including bacteria, viruses, and fungi. The microorganisms of the gastrointestinal tract are equivalent to about 4 kg of biomass. Everyone has a unique species composition [9]. The microbiota is essential for digestion and immunity and affects the brain and behavior [10,11] .

The intestinal microbiome is a crucial postnatal source of microbial stimulation of the immune system [11]. Current evidence supports the role of intestinal colonization in promoting and maintaining a balanced immune response in early life [11–13]. Certain intestinal microbial strains inhibit or attenuate the immune responses associated with chronic inflammation in experimental models [14].

The gut-lung axis ensures a bidirectional communication between these organs with microbial and immune interactions. The roles of bacterial and fungal elements are still under investigation, but in the long term, they could

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open the way for new approaches to managing respiratory diseases, such as asthma, COPD, and cystic fibrosis [12].

The personal microbiome has an essential role in the physiology of the human body. On the other hand, some studies demonstrated that bacterial or viral components could cause chronic inflammation and increase the risk of colon or lung cancer [15].

Lung Cancer Carcinogenesis

The most valuable indicator of clinical risk for carcinogenesis development is both direct exposures to smoking and second-hand exposure. Other risk factors in developing lung cancer are exposure to ionizing radiation, radon, and occupational exposure (chromium, nickel, asbestos). Additional risk factors are older age, male gender, or family history of lung cancer [3,16]. In smokers, a correlation has been demonstrated between the degree of nicotine addiction and the increase of specific biomarkers, such as IL 6, TNFα, C-reactive protein (CRP), and fibrinogen, which indicate the body's reactivity to the toxic effects of cigarette smoke and subsequently lead to subclinical changes responsible for future complications [17]. Nicotine stimulates nicotinic acetylcholine receptors and causes the release of dopamine, norepinephrine, acetylcholine, gamma-aminobutyric acid (GABA), and endorphins [18,19]. From the point of view of inflammation, smoking causes an impairment of the oxidant-antioxidant balance, demonstrated by increased lipid peroxidase metabolites and decreased antioxidant levels.

A multivariate analysis of the association of lung inflammation with the diagnosis of lung cancer revealed the most frequently involved biomarkers in carcinogenesis [20]. Soluble receptors represent them for interleukin 6 (IL-6), soluble vascular endothelial growth factor receptor 2,3 (sVEGFR2, sVEGFR3), Soluble tumor necrosis factor receptor I (sTNFRI); cytokines: Interleukin 10,21 (IL10, IL 21); chemokines [1–3].

The most frequently affected genes in non-small cell lung cancer are EGFR, ALK, ROS1, BRAF, MET, HER2, RET and NTRK1 mutations [21,22].

Genetic disorders in lung cancer pathophysiology

Small cell lung cancer

Tumor mutations in small cell lung cancer are directly correlated with smoking exposure [16], concomitant with the inactivation of two tumor suppressors, p53 and RB [23]. Transformations in the lung parenchyma and immune context are also essential for triggering carcinogenesis [23,24]. Other changes that appear in small cell lung cancer, along with the inactivation of these two tumor suppressors, are represented by the amplification of genes from the MYC family, as well as the amplification of FGFR1 (encoding fibroblast growth factor receptor 1) and GNAS (encoding the α-subunit of the heterotrimeric G protein Gs) [15,24,25].

Tumor cells from small cell lung cancer communicate with the microenvironment in an endocrine, paracrine, and autocrine manner. Neuropeptides produced by these tumor cells stimulate proliferation and inhibit cell apoptosis through autocrine and paracrine mechanisms [22–24].

Non-small cell lung cancer

The most common histological subtypes of non-small cell lung cancer (NSCLC) are represented by squamous cell carcinoma, adenocarcinoma, and large cell cancer. A significant percentage of these cases, approximately 70%, have genetic mutations, such as the EGRF (epidermal growth factor receptor) mutation in those with adenocarcinoma, anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1), Kirsten rat sarcoma virus (KRAS), V-RAF murine sarcoma oncogene homolog B1 (BRAF), MET or human epidermal growth factor receptor (HER2) [22,26,27].

Lung microbiome and lung cancer

The microbiome's involvement in neoplastic pulmonary pathology includes various pathophysiological ways [6,10]. The hypothesis that the microbiome can be directly oncogenic by stimulating mucosal inflammation and maintaining metabolic and immune dysfunctions has benefited from critical support [28]. Various microorganisms, such as *Haemophilus influenzae, Enterobacter species, Escherichia coli, Streptococcus pneumoniae,* or *Legionella*, can cause an inflammation associated with a pattern that can lead to bronchopulmonary cancer [6,10]. Investigations performed in the neoplastic lung process showed the presence of Streptococcus spp. and the absence of it in the unaffected lung [29].

Analysis of spontaneous sputum samples from lung cancer patients highlighted the predominance of pathogens such as *Granulicatella, Abiotrophia*, and *Streptococcus spp*, and analysis of the liquid from bronchoalveolar lavage revealed elevated levels of Firmicutes [7].

The identification of *Streptococcus* and *Veillonella* in patients with bronchopulmonary neoplasm has been associated with the activation of phosphoinositide 3-kinases, suggesting the role of microorganisms in proliferation, migration, and invasion [25]. Also, the presence of *Haemophilus influenza* suggested tumor proliferation mediated by interleukin 17C (IL 17C) and neutrophilic infiltration, adjacent to increased metastatic tumor masses in smoking patients with lung cancer [5].

Interrelations have been found between pulmonary microbiome dysbiosis and the appearance of neoplasms, bacterial infections being typical in patients with lung cancer [7,10]. Lung infections complicate the evolution of the disease in a significant percentage of neoplastic patients, and retro-stenotic pneumonia decreases the effectiveness of oncological treatment and inevitably decreases the survival of these patients [10]. The microbial etiology of this pneumonia is insufficiently known, which makes it challenging to administer targeted antibiotic therapy. Recent studies

have shown an association between local dysbiosis and the occurrence of lung cancer [30].

Among the involved bacterial subtypes, the *Thermus species* have been identified more frequently in patients with lung cancer in advanced stages, and *Legionella* was present in patients with lung metastases [10]. Isolation of *Veillonella* and *Capnocytophaga* in patients with bronchopulmonary neoplasm presents a high association with small cell carcinoma and adenocarcinoma [25,28]. Although the results were diverse according to the involved bacterial subtype, all these hypotheses from different studies are essential because the alteration of the lung microbiome in patients with bronchopulmonary cancer can lead to an unfavorable prognosis [31].

Studies in the literature analyzed the microbiota of the lower airways in patients undergoing diagnostic bronchoscopy for suspected lung cancer. They found that malignancy could be determined with 70% accuracy by isolating *Enterococcus, Capnocytophaga*, or *Actinomyces,* and the identification of *Microbispora* may be associated more frequently with benign lung diseases [32]. Also, *Veillonella* and *Megasphaera* genera can potentially serve as biomarkers for the occurrence of lung cancer [7]. Commensal bacteria are essential to maintain pulmonary homeostasis [7,32].

A higher diversity of the microbiome was associated with increased survival rates, which in the future could lead to significant results for increasing the quality of life and survival in patients with lung cancer from the perspective of personalized medicine for this pathology [27].

Identifying these mutations in the lung microbiome can be used as a biomarker for lung cancer screening and prevention.

Impact of the lung microbiome on lung cancer pathophysiology

The lung microbiome can contribute to the development of lung tumors either directly by acting on tumor cells or indirectly by modulating the tumor-associated immune response [25]. It can directly modulate oncogenic pathways leading to carcinogenesis. Dysbiosis in the vicinity of the tumor can affect oncogenic signals and the metabolism of tumoral cells [13,33]. The local microbiome of lung cancer patients causes stimulation of amino acid metabolism, lipid metabolism, and xenobiotic biodegradation [30,33].

The altered microbial metabolic profile can impact the gene expression of cells in the airway epithelium [10,34]. A structure of resident immune cells in the lungs maintains tissue homeostasis and supports immune defense in response to pathogens. The development of lung cancer is closely associated with chronic inflammation characterized by infiltration of inflammatory cells and accumulation of pro-inflammatory markers, including cytokines, chemokines, and prostaglandins that stimulate cell proliferation, angiogenesis, and tissue remodeling, or metastasis [10,35]. Although the source of inflammation is not identified, the influence of specific cellular and molecular mechanisms is to be determined to assess the evolution of this pathology [10,25]. It also becomes apparent that the specific bacterial population of the lung is essential for regulating lung inflammation, especially in the neoplastic context. Inhibition of antitumor immunity is associated with a shift from *Firmicutes* to *Proteobacteria* or other Gram-positive microbes [10,15,28].

The lung and gut microbiome can affect the immune response. Clinical evidence has demonstrated the different responses to immunotherapy of NSCLC patients depending on the microbiome alteration [26,32]. The gut-lung axis plays an essential role in carcinogenesis, being involved in various pathways. The lung microbiome can contribute to the development of lung cancer either directly by acting on tumor cells or indirectly by modulating the tumor-associated immune response. The gut microbiome can directly affect the response to immunotherapy in patients with non-small cell lung cancer [12].

These evidences demonstrates that there is a direct correlation between the lung microbiota, carcinogenesis and the appearance of metastases. From a pathophysiological point of view, these interrelations refer to the chronic inflammatory tumor response, the appearance of genetic mutations induced by bacterial components and a decrease in the local immune response. Lung microbiota can exert an important role in carcinogenesis, in the response to chemotherapy and immunotherapy [36].

The personalized evaluation of clinical and inflammatory risk and genetic mutations can lead to a pattern of the patient at risk of developing lung cancer, thus opening new perspectives for early diagnosis, targeted therapy, and implicitly for increasing survival and quality of life.

Authors' contribution

CEB: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published

IGC: revising the article, acquisition of data, analysis of data, final approval of the version to be published

HKS, AHS: drafting the article, interpretation of data, final approval of the version to be published

BLG: conception and design, acquisition of data, drafting the article, final approval of the version to be published

Conflict of interest

None to declare.

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