Airway Microbiota for Lung Cancer

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Recent research on cancer-associated microbial communities has elucidated the interplay between bacteria, immune cells, and tumor cells; the bacterial pathways involved in the induction of carcinogenesis; and their clinical significance. Although accumulating evidence shows that a dysbiotic condition is associated with lung carcinogenesis, the underlying mechanisms remain unclear. Microorganisms possibly trigger tumor initiation and progression, presumably via the production of bacterial toxins and other pro-inflammatory factors. The purpose of this review is to discuss the basic role of the airway microbiome in carcinogenesis and the underlying molecular mechanisms, with the aim of developing anticancer strategies involving the airway microbiota. In addition, the mechanisms via which the microbiome acts as a modulator of immunotherapies in lung cancer are summarized.

Keywords: microbiome ; lung cancer ; oncogenesis ; inflammation

1. Introduction

The human microbiome consists of more than 1000 species of bacteria inhabiting the human body, including the skin, oral cavity, nasal cavity, stomach, small intestine, large intestine, urinary tract, and vagina (hundreds of trillions of bacteria in number)[1]. Among them, the intestinal microbiome contains approximately 40 trillion bacteria, which exceeds the total number of human cells, and plays important roles in nutrient and energy consumption of the host. The human host and the intestinal microbiome are in a symbiotic relationship, which is mutually beneficial for maintaining homeostasis[2]. Intestinal bacteria metabolize substances that cannot usually be metabolized by the host to produce energy for self-maintenance, while the host uses these metabolites for its life activities. These bacteria also protect the host from invading foreign substances and pathogenic microorganisms[3]. Loss of this homeostasis leads to the development of various diseases, including cancer [4]. Currently, the roles of the intestinal and other microbiomes in malignant tumors are being actively investigated, and studies regarding their involvement in carcinogenesis and their application in cancer treatment and prevention are underway[5]. In particular, the intestinal microbiome has been shown to modify antitumor immune activity and play an important role in regulating response and resistance to immunotherapy in malignant tumors[6].

2. Development

The microbiome has been relatively well-studied in the context of obesity, inflammatory bowel disease, and arthritis. In oncology, the relationship between colorectal cancer (CRC) and certain microbiomes has been studied extensively[7][8]. Some studies have reported that microbes are involved in the malignant transformation of cells in the mucosa. In particular, the higher abundance of Fusobacterium nucleatum, a periodontal pathogenic bacterium colonizing the oral cavity, in the vicinity of tumors than around normal tissues in patients with CRC has prompted extensive research regarding their carcinogenesis-promoting property[7][8][9]. Studies have shown that the FadA adhesion protein complex (FadAc) expressed on the cell surface of F. nucleatum binds to the cell adhesion factor and E-cadherin on colonic epithelial cells to activate the β-catenin signaling pathway, thereby promoting cell proliferation[10]. In addition, F. nucleatum has also been shown to suppress antitumor immunity. Evidence suggests that F. nucleatum directly binds to T cell immunoreceptor with Ig and ITIM domains (TIGIT), an inhibitory receptor on human natural killer (NK) cells, via FAP2, thereby suppressing antitumor immunity and promoting development of CRC[11]. Higher F. nucleatum load has been associated with poor prognosis of CRC, suggesting the utility of this bacterium in predicting the progression and prognosis of this disease, as well as for developing strategies for its prevention and treatment[12].

Recent studies have revealed the presence of the microbiome in the lower respiratory tract; however, its association with the development and metastasis of lung cancer remains unclear. At the same time, advancements in gene analysis techniques have enabled analysis of the lower airway microbiome using 16S ribosomal RNA (rRNA) gene sequencing and metagenomic analysis, and the microbiome populations that may be involved in the development of lung cancer have

been identified[3]. These microbiomes may potentially act as novel diagnostic and therapeutic biomarkers, which may facilitate the development of personalized medicine[13]. This review outlines the current knowledge regarding the role of the lower airway microbiome in carcinogenesis.

3. Findings

The existence of microbiota in the lower airways has been demonstrated using novel sequencing techniques, and their pathological significance may vary with the host, lung biology, and exposure to microbes. Significant evidence supports the plausibility of this association with potential therapeutic implications. Whether modulation of microbiomes can lead to cancer prevention or treatment has not yet been established. The analysis-related issues to be addressed include selection of clinical samples, DNA extraction methods, platforms for 16S rRNA gene sequencing, and improvement of analytical techniques. The role of microbiomes in carcinogenesis is currently being investigated and remains to be completely elucidated. Future large-scale studies will provide new insights regarding the microbiome-based prevention and treatment of lung cancer.

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