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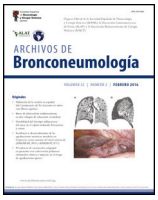

Editorial

Lung Cancer and Microbiome

Cancer de pulmon y microbioma

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The human microbiome comprises the collective genomes of all bacteria, archaea, eukaryotic viruses, bacteriophages, fungi and protozoa that colonize the body, acquired through vertical transmission and exposure to the environment.[1] The principal niches of microorganisms in the human body include the gastrointestinal tract, the oral cavity, the urogenital tract, the skin, and the upper and lower respiratory tracts. This complex ecosystem benefits the host by bioconverting nutrients and protecting against pathogenic microbes. Its imbalance, or dysbiosis, can ultimately lead to disease.

The microbiome has important immunomodulatory properties, conferring benefits or disease susceptibility to the body. The intestinal microbiota shapes the innate and adaptive immune responses against inflammation, infections, and favours commensal tolerance.[2] It is known that the imbalance of the human microbiome or dysbiosis occurs in systemic diseases such as diabetes and chronic gastrointestinal diseases. And there are numerous evidences of its vital role in carcinogenesis, due to direct oncogenic effects, generation of trophic factors, and metabolic, inflammatory and immunomodulatory changes. The alteration of the microbiota by the chronic use of certain antibiotics has been associated with an increased risk of cancer development.[3] The impact of the intestinal microbiome has been widely demonstrated in the case of digestive cancer, as the transfer of wild-mice gut microbiota into C57BL/6 laboratory mice protects them from viral infection and gastrointestinal cancer.[4] In lung cancer, recent studies have shown that local microbiota dysbiosis and inflammation also correlates with cancer development via T-cells.[5] Searching for specific biomarkers, a study of the microbiome in bronchoalveolar lavage fluid identified *Veillonella* and *Megasphaera* as more abundant in lung cancer than in benign lesions.[6] A meta-analysis of epidemiologic studies analyzed previous lung infections as risk factors for lung cancer. The relationship between infection by *Chlamydia pneumoniae* or *Mycobacterium tuberculosis* and an increased risk of lung cancer was studied (in 22 and 30 published studies, respectively). The results showed that a previous infection with either microorganism associated with an increased risk of lung cancer.[7] There are also microorganisms that confer protection against lung cancer, as *Lactobacillus*, that seems to have a therapeutic effect in a lung cancer mouse model.[8] Regarding the mechanism for dysbiosis, it seems that many byproducts of the host inflammation are growth factors for *Gamma proteobacteria*. These bacteria create a chronic inflammatory environment that promotes proliferation and survival of malignant cells, aberrant angiogenesis, and tumour metastasis. However, the deleterious effect that pathogenic microbiota exerts in the organism can be counteracted. A study investigated the role of the microbiome existing in the host in the carcinogenesis of lung cancer, using mice. For the study, a group of mice was subjected to urethane-induced lung adenocarcinoma, and was later administered with prebiotics by oral gavage, compared to control group. The result of the study revealed that the presence of *Clostridiales* and *Lachnospiraceae* families was lower in both lung and intestinal tracts in mice with induced lung adenocarcinoma, and that *S24-7*, *Bacteroidales* and *Firmicutes* were more abundant in their intestinal tract. All of them returned to normal levels after prebiotics administration, indicating a possible therapeutic approach.[9]

Not only the microbiome has a role in the generation and progression of cancer, but it can also influence the response to chemotherapies and immunotherapies. Therefore, the microbiome manipulation in anticancer therapies has been explored under different perspectives. On the one hand, by direct modulation of the carcinogenic potential of the microbiome, either blocking the production of oncogenic bacterial products or inhibiting the production of bacterial enzymes that convert anticancer drugs into toxic products.[10,11] A rational modulation of the microbiota with specific antibiotics could therefore have a positive effect in certain oncologic therapies.[3] On the other hand, several studies demonstrate a diminished effect of certain anti tumour chemotherapies and immunotherapies in germ-free mice, as well as in mice treated with wide-spectrum antibiotics. The modification of the microbiota

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by the use of certain antibiotics has been associated with a reduction in the clinical benefit of therapies with immune checkpoint inhibitors -such as PD-L1 and CTLA4 blockade- in Non-Small-Cell Lung Cancer (NSCLC).[3,12] The fact that specific intestinal commensal bacteria boost the antitumoral responses of the host even in distal locations of the organism lays the foundation of their role in the efficacy of cancer immunotherapies.[3,13] In NSCLC, the efficacy of CTLA-4 blockade was associated with T-cell responses specific for *Bacteroides fragilis* or *Bacteroides thetaiotaomicron*.[14] Regarding PD-1/PD-L1 blockade therapy, an important study suggested that patients with NSCLC can be stratified into responders and non-responders, based on the composition of their gut microbiota. This study analysed the faecal microbiota of 153 patients with NSCLC, finding more bacteria from *Akkermansia muciniphila* in the anti-PD-L1 responders.[15] The tumours from mice that received a Faecal Microbial Transplantation (FMT) from responders showed a higher density of antitumour $CD8^+$ T-cells, while tumours of mice that received transplant from non-responders showed more immunosuppressive $CD4^+$ T-reg cells.

Therefore, the manipulation of the microbiota seems to be a promising strategy to develop novel therapeutic approaches in both prevention and treatment of lung cancer. The most important characteristic observed in responders to immunotherapy is their ratio of favourable/not-favourable bacteria.[13] It is not clear if a positive response can be caused by a single microorganism or even by a combination. Most likely would be influenced by the interaction of several species with the host, involving complex ecological and metabolic changes, that ultimately affect cancer immunity. The mechanism by which favourable bacteria help the efficacy of immunotherapy seems to be that they support the priming of the T-cells against tumour antigens. In order to improve this equation by increasing favourable bacteria, different strategies can be used: (i) FMT using as donor a patient that has previously responded to therapy anti-PD-1. (ii) The administration of probiotics as dietary supplements. Not only introducing traditional beneficial bacteria such as Bifidobacterium and lactic acid-producing bacteria, but also next-generation beneficial bacteria such as *A. muciniphila*, that have been introduced in preclinical trials with success.[15]

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