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PRESS RELEASE

ANTIBIOTICS AFFECT THE EFFICACY OF IMMUNOTHERAPY

A study published in the journal *Science* by a research team from Gustave Roussy, INSERM, INRA, AP-HP, IHU Médiaterranée Infections* and Paris-Sud University shows that prescribed antibiotics impair the efficacy of immunotherapy in cancer patients. It is important to consider that more than 20% of patients living with cancer receive antibiotics. The authors explored patients' gut microbiota composition by metagenomic analysis and demonstrated that the bacterium *Akkermansia muciniphila* was associated with a better clinical response to anti-PD-1 antibody immunotherapy. Moreover, oral administration of this bacterium to mice with an unfavorable microbiota restored the anti-tumor activity of the immunotherapy.

This paper will be published online by the journal Science on Thursday, 2 November 2017.

Immunotherapy represents a real revolution in cancer therapies and has been shown to be superior to standard chemotherapy in advanced melanoma, lung, renal and bladder cancer. Although a large proportion of patients still do not benefit from this treatment, "*Our research partially explains why some patients do not respond. Taking antibiotics has a deleterious impact on survival in patients receiving immunotherapy. Furthermore, the composition of the intestinal microbiota is a new predictive factor for success,*" summarized Dr. Bertrand Routy, hematologist and member of the team of Professor Laurence Zitvogel, director of the "Immunology of tumors and immunotherapy" laboratory (Inserm/Paris-Sud University/Gustave Roussy).

In a cohort of 249 patients treated with anti-PD-1/PD-L1 based immunotherapy for advanced lung, kidney or bladder cancer, 28% received antibiotics for minor infections (dental, urinary or lung infections) but their general health status was not different from patients not receiving antibiotics. The study's findings revealed that taking antibiotics two months before and up to one month after the first treatment had a negative effect on progression-free survival and/or overall survival for these three types of cancer.

// Favorable microbiota determined by metagenomics

The precise composition of the gut microbiota was established by metagenomics both before and during immunotherapy in 153 patients with advanced lung or kidney cancer. The identification of all the bacterial genes present in the gut microbiota was performed by INRA (MetaGenoPolis, Dr. Emmanuelle Le Chatelier). A favorable microbiota composition, rich in

Akkermansia muciniphila, was found in patients with the best clinical response to immunotherapy and in those whose disease had not progressed for at least 3 months.

// Improving unfavorable microbiota

To demonstrate a direct cause and effect relationship between the composition of gut microbiota and the efficacy of immunotherapy, favorable microbiota (taken from patients who had a good response to PD-1 immunotherapy) and unfavorable microbiota (from patients with therapeutic failure) were transferred to mice deprived of gut microbiota. The mice receiving the favorable microbiota did better when treated with immunotherapy than those who received the unfavorable microbiota. In the latter group, oral administration of *Akkermansia muciniphila* resulted in the restoration of the efficacy of anti-PD-1 immunotherapy. Changing the microbiota in the mouse re-established the effectiveness of immunotherapy by activating certain immune cells.

Results simultaneously reported in the same edition of the journal by an American team (Dr. Jennifer Wargo, MD Anderson, Texas) support these findings showing that the composition of microbiota in melanoma patients predicts the response to anti-PD-1 immunotherapy.

This research is being carried out within the framework of the Torino-Lumière project (a 9 M€ "investissement d'avenir" [investment for the future] program). The objective of this unique study is to develop microbiome-based biomarkers that predict the response to immunotherapy in patients with lung cancer. This prospective multicenter study initiated in 2016 aims at determining unfavorable bacterial signatures to compensate patients with a combination of bacteria endowed with immunotherapeutic properties.

About immunotherapy

Immunotherapy has changed the way we treat various cancers. These novel immunotherapies include monoclonal antibodies (anti-CTLA4 or anti-PD1), transferring activated T-lymphocytes and bispecific agents, all boosting patient's immune system. They not only reduce tumor size but also, and for the first time, significantly increase patient overall survival, eventually curing metastatic or locally advanced cancers in melanoma.

About gut microbiota

Gut microbiota (previously known as intestinal flora) represents a complex ecosystem consisting of 100,000 billion bacteria, viruses, archaea, parasites and yeasts. They colonize the bowel from birth and participate in the maturation of immune defense mechanisms. Individuals have their own specific microbiota. Its composition is a product of genetic, nutritional and environmental factors.

* Gustave Roussy = Leading comprehensive cancer center in Europe

INSERM = National Institute for Health and Medical Research

INRA = National Institute for Agronomic Research

AP-HP = Paris Public Hospitals

IH Méditerranée Infections

Source

Gut microbiome influences efficacy of PD-1 based-immunotherapy against epithelial tumors

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