Villejuif, November 2nd 2017

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 Mediterranée Infections

Source

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

Science, publication advanced online,

Bertrand Routy[1,2,3], Emmanuelle Le Chatelier[4], Lisa Derosa[1,2,3], Connie P. M. Duong[1,2,5], Maryam Tidjani Alou[1,2,3], Romain Daillère[1,2,3], Aurélie Fluckiger[1,2,5], Meriem Messaoudene[1,2], Conrad Rauber[1,2,3], Maria P. Roberti[1,2,5], Marine Fidelle[1,3,5], Caroline Flament[1,2,5], Vichnou Poirier-Colame[1,2,5], Paule Opolon[6], Christophe Klein[7], Kristina Iribarren[8,9,10,11,12], Laura Mondragón[8,9,10,11,12], Nicolas Jacquelot[1,2,3], Bo Qu[1,2,3], Gladys Ferrere[1,2,3], Céline Clémenson[1,13], Laura Mezquita[1,14], Jordi Remon Masip[1,14], Charles Naltet[15], Solenn Brosseau[15], Coureche Kaderbhai[16], Corentin Richard[16], Hira Rizvi[17], Florence Levenez[4], Nathalie Galleron[4], Benoit Quinquis[4], Nicolas Pons[4], Bernhard Ryffel[18], Véronique Minard-Colin[1,19], Patrick Gonin[1,20], Jean-Charles Soria[1,14], Eric Deutsch[1,13], Yohann Loriot[1,3,14], François Ghiringhelli[16], Gérard Zalcman[15], François Goldwasser[9,21,22], Bernard Escudier[1,14,23], Matthew D. Hellmann[24,25], Alexander Eggermont[1,2,14], Didier Raoult[26], Laurence Albiges[1,3,14], Guido Kroemer[8-12,27,28]*, and Laurence Zitvogel[1,2,3,5]*.

[1]Gustave Roussy Cancer Campus (GRCC), Villejuif, France.
[2]Institut National de la Santé Et de la Recherche Médicale (INSERM) U1015, Villejuif, France. Equipe Labellisée—Ligue Nationale contre le Cancer, Villejuif, France.
[3]Univ. Paris-Sud, Université Paris-Saclay, Gustave Roussy, Villejuif, France.
[4]MGP MetaGénoPolis, INRA, Université Paris-Saclay, Jouy-en-Josas, France.
[5]Center of Clinical Investigations in Biotherapies of Cancer (CICBT) 1428, Villejuif, France.
[6]Gustave Roussy, Laboratoire de Pathologie Expérimentale, 94800 Villejuif, France.
[7]Centre de Recherche des Cordeliers, INSERM, Université Paris Descartes, Sorbonne Paris Cité, UMRS 1138, Université Pierre et Marie Curie Université Paris 06, Sorbonne Universités, Paris, France.
[8]Metabolomics and Cell Biology Platforms, GRCC, Villejuif, France.
[9]Paris Descartes University, Sorbonne Paris Cité, Paris, France.
[10]Equipe 11 Labellisée—Ligue Nationale contre le Cancer, Centre de Recherche des Cordeliers,Paris, France.
[11]Institut National de la Santé et de la Recherche Médicale, U1138, Paris, France.
[12]Pierre et Marie Curie University, Paris, France.
[13]Department of Radiation Oncology, Gustave Roussy, Université Paris-Saclay, F-94805 Villejuif, France; INSERM U1030, Molecular Radiotherapy, Gustave Roussy, Université Paris-Saclay.
[14]Department of Medical Oncology, Gustave Roussy, Villejuif, France.
[15]Thoracic Oncology Department-CIC1425/CLIP2 Paris-Nord, Hospital Bichat-Claude Bernard, AP-HP, University Paris-Diderot.
[16]Department of medical oncology, Center GF Leclerc, Dijon, France.
[17]Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[18]Molecular Immunology and Embryology, UMR 7355, CNRS, University of Orleans, Orléans, France.
[19]Department of Pediatric Oncology, GRCC, Villejuif, France.
[20]Preclinical Research Platform, GRCC, Villejuif, France.
[21]Department of Medical Oncology, Cochin Hospital, Assistance Publique—Hôpitaux de Paris, Paris, France.
[22]Immunomodulatory Therapies Multidisciplinary Study group (CERTIM), Paris, France
[23]Institut National de la Santé Et de la Recherche Medicale (INSERM) U981, GRCC, Villejuif, France.
[24]Department of Medicine, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[25]Department of Medicine, Weill Cornell Medical College, New York, NY, USA.
[26]URMITE, Aix Marseille Université, UM63, CNRS 7278, IRD 198, INSERM 1095, IHU - Méditerranée Infection, 19-21 Boulevard Jean Moulin, 13005 Marseille
[27]Pôle de Biologie, Hôpital Européen Georges Pompidou, Assistance Publique—Hôpitaux de Paris, Paris, France.
[28]Department of Women's and Children's Health, Karolinska University Hospital, 17176 Stockholm, Sweden.