ONCOBIOME

Microbiota against cancer
International research program

REVIEW #4

February 2021

First and bigger network and biobanking of cancer patients stools for building up gut oncomicrobiome signatures for a better diagnosis and treatment of malignancies in Europe.

SPECIAL EDITION

Back on 2 major ONCOBIOME publications

ONCOBIOME is happy to herald that two major pieces of work were published in the international litterature.
These two papers have been conducted by the coordinator, Pr. Zitvogel, in close collaboration with the University of Trento (in partnership with Dr. Nicolas Segata), University of Paris and INSERM (Pr. Guido Kroemer), CHUM University of Montreal, Canada, and the President of our ONCOBIOME scientific advisory board, from Harvard Medical School, US (Pr. Zoltan Szallasi).

Prof. Laurence Zitvogel
Gustave Roussy - Villejuif, France

Nature Medicine

Roberti PM et al.

Metastatic proximal colon cancers represent the third cause of death by cancer achieving clinical benefit to immunotherapy in these patients is currently an unmet medical need.

Why DNA mismatch repair-proficient or microsatellite-stable proximal colon cancers (CC), endowed with tumor infiltrating lymphocytes and treated with oxaliplatinum-based chemotherapy (FOLFOX or FOLFIRINOX), a cytotoxic compound mediating immunogenic cell death, fail to benefit from immune checkpoint blockade?

The molecular and cellular cues underlying the delicate equilibrium between tolerance *(vis-à-vis of self and food antigens)* and immunity *(against pathogens and tumors)* in the intestinal barrier have always been an immunological challenge. Roberti PM et al. shed some light as to how ileal bacteria may contribute to break tolerance to self antigens shared between ileal crypts and cancer stem cells within CC.

Roberti PM et al. reported that the immunogenicity of ileal epithelial cell death mediated by OXA to treat a proximal CC relied on two biological features:
(1) antigenicity provided by the caspase 3/7-dependent apoptosis of crypt-derived intestinal epithelial cells (IEC)
(2) the adjuvanticity of selected ileal bacterial families or species (Erysipelotrichaceae, B. fragilis).

These features cooperated to elicit TFH immune responses (CD4+ T cells expressing CXCR5, PD1 and Bcl6 and orchestrating B cell maturation for antibody production) and antibody producing cells protective against tumor progression.

A vaccine composed of OXA-exposed dying ileal (and not colonic) IEC was more effective to immunize naive hosts against a lethal dose of colon cancer cells when admixed with immunogenic ileal bacteria (such as Bacteroides fragilis or Erysipelatoclostridium ramosum) capable of boosting TFH and B cell responses than tolerogenic ones (such as Fusobacterium nucleatum or Prevotella clara) that failed to do so, favoring TH17 responses that are protumorigenic.
Roberti et al. postulated that PD-1 expressing TFH induced by OXA-mediated ileal apoptosis could be bolstered by anti-PD-1 Abs and carried out to modulate the efficacy of a combination of OXA with this immune checkpoint inhibitor with a concomitant oral gavage with immunogenic (B. fragilis, C. ramosum) versus tolerogenic (F. nucleatum, P. clara) bacteria in MSS and MSI mouse colon cancers. They could bring evidence that the ileal residence and/or colonization of bacteria fostered (as for B. fragilis, C. ramosum) or blunted (as for F. nucleatum, P. clara) the immunostimulatory anticancer effects of the combinatorial regimen.

These additive/synergistic effects of both therapeutic modalities pave the way to pre-selecting pCC patients based on their ileal microbiome prior to therapy and encourage the screening of cytotoxicants capable of inducing ileal apoptosis and a favorable shift of the ileal microbiome.

Vaccines composed of autologous apoptotic ileal enteroids could protect individuals and families diagnosed with a Lynch syndrom, a hereditary form of pCC cancer.

Roberti, M.P., Yonekura, S., Duong, C.P.M., Picard, M., Ferrere, G., Tidjani Alou, M., Rauber, C., Iebba, V., Lehmann, C.H.K., Amon, L., et al. (2020). Chemotherapy-induced ileal crypt apoptosis and the ileal microbiome shape immunosurveillance and prognosis of proximal colon cancer. Nat. Med. 26, 919–931.

Sciences

Fluckiger A et al.

This paper addressed how intestinal microbes can possibly raise an immune response against distinct tumors.

Mechanistically, immunogenicity results from antigenicity and adjuvanticity, meaning that anticancer probiotics might provide both components to the immune system to prime T cell responses. In fact, we recently identified a H-2Kb-restricted epitope derived from a Siphoviridae phage which can lysogenize distinct strains of E. hirae in mice and E. faecalis in humans (Fluckiger, Science Aug 21, 2020).

This antigen contained within the tape measure protein (TMP) of the enterophage shares a 78% molecular mimicry with an oncogenic driver, the proteosomal subunit PSMB4, over-expressed in certain mouse tumors. TMP-specific, H-2Kb restricted CD8+ T cells elicited in the spleen after oral gavage with E. hirae 13144 (EH13144) during cyclophosphamide therapy cross-reacted with tumor cells expressing PSMB4, contributing to keep in check tumor growth (Fluckiger, Science Aug 21, 2020).

We found that this TMP enterophage protein also harbors high degree of homology with an HLA-A2-restricted epitope in humans, within a tumor suppressor, called GPD1L, involved in the HIF1a-dependent hypoxia circuitry. Lung and kindey cancers overexpressing GPD1L have a better prognosis and a superior response rate to anti-PD1 Ab-based immunotherapy.

Similarly, patients harboring E. hirae or E. faecalis lysogenized with the enterophage, and bearing the TMP sequence, experienced a clinical benefit to PD1 blockade in contrast to those who did not. We extended these exemplifications of T cell clones recognizing tumor epitopes sharing molecular mimicry with bacterial or phage antigens to famous naturally processed melanoma antigens (such as MelanA/MART1).

Therefore, we concluded that cross-reactive T cells that have been primed in the intestines from birth or during life and maintained in the gut associated lymphoid tissues might be able to recirculate and be mobilized against transformed cells overexpressing self antigens in molecular mimicry with the intestinal microbiome. Given the 1013 bacteria and 1031 phage residing in our intestines and all the ununknown overwhelming our mammalian part, we surmise that this demonstration will open up new avenues for T cell therapy and vaccination beyond the neoantigens.

Fluckiger A., R. Daillère, M. Sassi, B.S. Sixt, P. Liu, F. Loos, C. Richard, C. Rabu, M.T. Alou ,A.G. Goubet, F. Lemaitre, G. Ferrere, L. Derosa, C.P.M Duong, M. Messaoudene, A. Gagné, P. Joubert, L. De Sordi, L. Debarbieux, S. Simon, C.M. Scarlata, M. Ayyoub, B. Palermo, F. Facciolo, R. Boldot, R. Wheeler, I.G. Bonoca, Z. Sztupinszki, K. Papp, I. Csabai, E. Pasolli, N. Segata, C. Lopez-Otin, Z. Szallasi, F. Andre, V. Iebba, V. Quiniou, D. Klatzmann, J. Boukhalil, S. Khelaifia, D. Raoult, L. Albiges, B. Escudier, A. Eggermont, F. Mami-Chouaib, P. Nistico, F. Ghiringhelli, B. Routy, N. Labarrière, V. Cattoir, G. Kroemer, L. Zitvogel. 2020. Cross-reactivity between tumor MHC class I-restricted antigens and an enterococcal bacteriophage. Science. 369:936-942. doi: 10.1126/science.aax0701.

VISIT THE ONCOBIOME WEBSITE

Visit **www.oncobiome.eu** to be uptated on the latest ONCOBIOME news.

KEY DATES

Meet - virtually - the ONCOBIOME team at the following events and learn more about the consortium:

- EACR / June 20th – 23th
- IHMC / June 27th – 29th

KEY FIGURES

18
teams across 9 European countries and Montréal

9000
cancer patients

25 000
stool biobanking

15
million euros

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Se désinscrire

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