The dirty secrets of cancer immunology: links between gut microbiota and tumor immunosurveillance

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Abstract

We and others attempted to demonstrate the critical impact of intestinal commensals in cancer immunosurveillance, in particular in eliciting protective innate and cognate immune responses during anti-cancer therapies. One of the most striking discoveries originated from the description of the immunosuppressive role of antibiotics (ATB) on immune checkpoint inhibitors (ICI) in oncology. First, ATB drastically reduce the efficacy of immunotherapy targeting CTLA4 or PD-1/PD-L1 in lung and kidney patients. Secondly, metagenomics analyses of feces at diagnosis predict therapeutic failure to immunotherapy. Third, fecal microbial transfer of stools from responding or resistant cancer patients into germ free "avatar" tumor bearing rodents confers sensitivity or resistance to anti-PD1/PDL-1 Abs in recipients respectively. Next, we identified various mechanisms accounting for the links between the gut microbiome and antitumor immunosurveillance: 1/ cancer causes a beta-adrenergic receptor-dependent stress ileopathy triggering the intestinal dysbiosis and contributing to tumor progression, requiring specific therapies 2/ isolation of a group of "immunogenic commensals" (such as *Akkermansia muciniphila, B. fragilis, Enterococcus hirae* and its enterophage, *Alistipes shahii, Ruminococcus spp*) capable of mounting IL-12-dependent immune responses mediated by Follicular T helper cells, in play during oxaliplatinum or cyclophosphamide and immune checkpoint blockade, 3/ demonstration of molecular mimicry between microbial antigens (an enterococcus phage) and cancer epitopes recognized by CD8+ T effector cells that account for the immunogenicity of some bacterial species (in mice and patients), 4/ the immunosuppressive role of harmful pathobionts such as *Enterocloster gen. (Clostridium clostridioformis/ bolteae)*, dominant after ATB stop promoting the gut exodus of regulatory T cells towards tumor beds. Moreover, we reported that tertiary lymphoid organs that are associated with long term benefit to PD1 blockade are associated with proficient immune responses directed against pathobionts invading cancer cells in urothelial carcinoma. Finally, we unveiled that MAdCAM-1 is a gut immune checkpoint keeping in check the exodus of Tr17 regulatory T cells to tumor beds. Finally, we are now describing a diagnosis tool of intestinal dysbiosis (based on the relative abundance of fecal *Akkermansia* spp together with the "Toposcore" at baseline prior to therapy), predicting resistance to PD1 blockade in lung cancer patients. These discoveries have seminal clinical implementations, in that they led to proof-of-concept trials that primary resistance to ICI in stage IV melanoma can be circumvented by fecal microbial transplantation (FMT) from cured donors along with the reintroduction of the same ICI.

Biography

Prof. L. Zitvogel, MD (Clinical Oncology), PhD (Tumor Immunology), full professor at the University Paris Saclay, graduated in Medical Oncology in 1992. Scientific career first at the University of Pittsburgh, US. Became Research Director at Institut National de la Santé et Recherche Médicale U1015, and Scientific Director of the Clinicobiome program at Gustave Roussy, the largest cancer Center in Europe in 1998. Actively contributed to the field of cancer immunology and immunotherapy. Pionner of the concepts of immunogenic cell death and gut microbiota in cancer immunosurveillance and therapies. Recipient of many awards: Translation Research INSERM Prize, the ASCO-SITC, Brupbacher Awards 2017, ESMO Immuno-Oncology Award 2017, Baillet Latour Prize 2019, the Griffuel Prize 2019, the Duquesne Ligue Prize, and ITOC9 german award. Knighted Officer of Légion d'Honneur by French Ministery of Health 2019 and elected member of the National Academy of Medicine 2021. Her H-factor is 145, with >500 publications on PubMed, 108 265 citations in Clarivate analytics (highly cited researchers 2021, 2020, 2019, 2018, 2017, 2016).