

Microbiome and Other Environmental Factors

1541

STABILITY OF THE GUT MICROBIOTA DURING ANTI-PD1 IMMUNOTHERAPY DEFINES COMPLETE RESPONSE IN MELANOMA PATIENTS

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Background The advent of immune checkpoint inhibition (ICI) therapy markedly improved the outcome for melanoma. However, response remains heterogeneous, with about half of the patients being refractory or developing relapse. Although a causal link between the gut microbiota and modulation of antitumor response has been established, current knowledge is limited to findings from cross-sectional analyses. Here, we follow the gut microbiota of melanoma patients over the course of anti-PD1 therapy, to delineate gut changes related to host response and identify gut and host factors involved.

Methods To study response-related gut microbiota changes during ICI, patients with unresectable melanoma from two Italian hospitals (n=23) were followed at baseline and over the course of anti-PD1 immunotherapy (n=13 months) to collect fecal and blood samples along with clinical information. Patients were annotated by PFS and RECIST 1.1. Additionally, baseline fecal samples from tumor-free subjects were used as reference to compare gut diversity trends between response groups at therapy. Finally, cross-study validation was carried on metagenomes (n=281) from Europe (n=4), UK (n=2) and USA (n=3) baseline cohorts.

Results Our results demonstrate that the gut microbiota is fairly variable during ICI therapy; however, changes are less pronounced among complete responders (CR), especially at later cycles. We identify and validate longitudinally stable gut microbiota taxa in CR, which comprise mostly Clostridia taxa. These stable CR taxa associate consistently with positive systemic markers, supporting their immunomodulatory potential. At the functional level, our data demonstrate a key role for specific bacterial metabolic activities and structural components in driving a productive immune response. Here, we will present also experimental validation.

Conclusions Overall, we propose microbiota stability during ICI therapy as a consequential feature of an immune-beneficial Clostridia-rich gut among complete responders, which exploits bacterial metabolic activities and tumor antigen's cross presentation.

Ethics Approval Collection of data included in this study has been approved by the local Ethical Committee of the European Institute of Oncology (R845/18-IEO 889) and the Istituto Nazionale Tumori IRCCS Fondazione G. Pascale (37/22 oss).

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.1541>