TUMOUR MICROENVIRONMENT

Microbiota and immune cell interplay

Dysbiosis of commensal microbiota can contribute to cancer onset, progression and therapy response through effects on antitumour immunity. Two independent studies have now advanced our understanding of local microbiota immunomodulation and provided insight into how potential manipulation of microbial composition could transform treatment strategies for patients with cancer.

Whether local microbiota can influence lung cancer development is unknown. Using a genetically engineered mouse model of human lung adenocarcinoma induced by expression of *Kras*^{G12D} and deletion of *Trp53* in lung epithelial cells, Jin et al. compared tumour initiation and progression in germ-free (GF) and specific pathogen-free (SPF) control conditions. This revealed that both tumour growth and burden were decreased in GF mice in contrast to SPF mice. Analysing the bacterial composition from the bronchoalveolar lavage fluid of mice showed that there was expansion of the total bacterial burden as well as limited bacterial diversity in tumour-bearing SPF mice compared with non-tumour-bearing SPF controls. In particular, the taxa *Herbaspirillum* and Sphingomonadaceae were enriched in tumour-bearing lungs.

Accompanying the elevated bacterial abundance in tumour-bearing lungs of SPF mice was an increase in expression of genes encoding the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-23, known to be produced by myeloid cells in response to microbial exposure, as well as an expansion of lung-resident γδ T cells. Accordingly, these phenotypes were absent from tumour-bearing GF lungs.

The tumour-associated γδ T cells displayed a unique gene expression signature distinguished by strong expression of effector molecules with the potential to stimulate tumour-promoting inflammation and tumour cell proliferation. Moreover, the majority of these γδ T cells were defined as Vγ6$^+$Vδ1$^+$ γδ T17 cells as they secreted the pro-inflammatory cytokine IL-17A. Concomitant with the expanded population of γδ T cells was an increased infiltration of neutrophils into lung tumours compared with healthy lungs of SPF mice. Inhibition of γδ T cells using monoclonal antibodies depleted IL-17A levels, neutrophil accumulation and tumour cell proliferation, indicating mechanistically how microbiota-induced γδ T cells could shape lung cancer development.

Notably, the authors found a correlation between imbalances of bacterial taxa and lung cancer in humans when analysing The Cancer Genome Atlas data of non-small-cell lung cancer samples compared with normal lungs.

Several studies have shown that the composition of the gut microbiota can determine the clinical response to immune checkpoint inhibitors. Tanoue, Morita et al. used a rational approach to isolate commensal bacterial strains from the human microbiota that could specifically induce the accumulation of interferon-γ (IFNγ)$^+$ CD8$^+$ T cells, implicated in the efficacy of immunotherapy. Starting with human faecal samples from six healthy volunteers orally administered to GF mice, a sequence of selection steps was applied to obtain mice colonized in the intestines with human microbiota enriched in IFNγ$^+$ CD8$^+$ T cells-inducing species. From these mice, a mixture of 11 bacterial strains was selected on the basis that its inoculation into GF mice enhanced IFNγ$^+$ CD8$^+$ T cell frequency to the largest extent.

Besides increased colonic induction of IFNγ$^+$ CD8$^+$ T cells, the 11-strain mixture was also capable of inducing localized CD4$^+$ T cells at this site as well as systemic accumulation of IFNγ$^+$ CD8$^+$ T cells in other organs, possibly via circulating metabolites produced by the 11 strains. The authors established that the mechanistic link between colonic IFNγ$^+$ CD8$^+$ T cell accumulation and the 11-strain mixture was a combination of recruitment through IFNγ-mediated chemokine secretion from colonic epithelial cells, active proliferation and bacterial antigen-associated differentiation. Moreover, the 11-strain mixture could condition colonic CD103$^+$ dendritic cells to induce IFNγ$^+$ CD8$^+$ T cells through major histocompatibility complex class Ia expression.

> “manipulation of microbial composition could transform treatment strategies for patients with cancer”

To test the therapeutic potential of the 11-strain mixture, GF mice or GF mice colonized with the 11-strain mixture were subcutaneously engrafted with mouse MC38 colon adenocarcinoma cells followed by intraperitoneal injection with a programmed cell death 1 (PD1) antibody. Supplementation with the 11-strain mixture was sufficient to increase the therapeutic efficacy of the PD1 antibody compared with GF mice alone. Importantly, the 11-strain mixture could also inhibit tumour growth even without anti-PD1 treatment.

As most of the 11 strains were found to be rare and of low abundance in the human microbiome, these results suggest the tailored mixture may be a suitable candidate for the development of oral bacterial therapeutics to treat cancer.

These studies together exemplify how a finely tuned microbial balance can dictate tumour-promoting inflammation or antitumour immunity.

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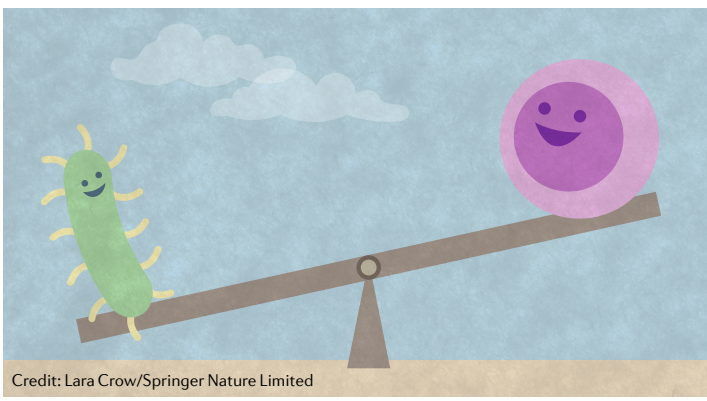
ORIGINAL ARTICLES Jin, C. et al. Commensal microbiota promote lung cancer development via γδ T cells. *Cell* https://doi.org/10.1016/j.cell.2018.12.040 (2019) | Tanoue, T. et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* **565**, 600–605 (2019)



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