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MICROBIOME

Gut microbiota sways response to cancer immunotherapy

There is increasing evidence that the intestinal microbiota can influence the outcome of cancer immunotherapy. The administration of inhibitors that target immune checkpoints (negative regulators of the immune system), such as the programmed cell death protein 1 (PD1)–PD1 ligand 1 (PDL1) axis, is a promising approach for the treatment of certain cancers, but the efficacy of immune checkpoint inhibitors in patients is heterogeneous. Preclinical studies in mice suggest that the intestinal microbiota can modulate responses to anti-PD1 therapy through interactions with the host immune system; however, this had not been investigated in humans. Now, three studies provide new evidence that the intestinal microbiota affects the outcome of anti-PD1 immunotherapy in patients with cancer.

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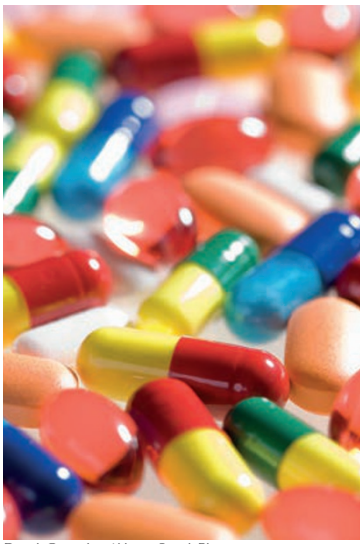

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In one study, Gopalakrishnan et al. surveyed the intestinal and oral microbiome of individuals that were treated for melanoma with anti-PD1 therapy and observed differences in the diversity and composition of the intestinal microbiome in individuals that responded to treatment versus non-responders. Individuals that responded to treatment had higher within-sample diversity of their intestinal microbiome and a higher abundance of bacteria from the Ruminococcaceae family and the *Faecalibacterium* genus. By contrast, non-responders had a lower within-sample diversity of their intestinal microbiome and had a higher abundance of members of the Bacteroidales order.

Matson et al. also observed associations between the intestinal microbiome composition and the response to anti-PD1 therapy in individuals with metastatic melanoma. Eight species were enriched in faecal samples of those individuals who responded to treatment, including *Bifidobacterium longum*, which is associated with responsiveness to cancer immunotherapy in mice. Two species — *Ruminococcus obeum* and *Roseburia intestinalis* — were more abundant in non-responders. In a study by Routy et al. that investigated interactions between PD1-based immunotherapy and the gut microbiota in individuals with epithelial tumours, they similarly observed a more diverse intestinal microbiome in responders. Furthermore, there was a marked increase in the abundance of *Akkermansia muciniphila* in patients that benefited the most from PD1 inhibition. Routy et al. also observed that exposure to antibiotics during treatment decreased the probability of responding to therapy, suggesting that the overall diversity of the microbiota and the presence of specific clades determine the responsiveness to immunotherapy.

In all three studies, faecal microbiota transplantation (FMT) to germ-free mice from individuals that responded to anti-PD1 therapy led to enhanced antitumour immunity compared with mice that received FMT from non-responder donors; mice that received FMT from responders had increased levels of antitumour $CD8^+$ T cells, whereas those that received FMT from non-responders had higher levels of immunosuppressive $CD4^+$ T cells.

Together, these studies suggest that the intestinal microbiota has an important mechanistic role in antitumour immunity, which has implications for the use of immune checkpoint inhibitors to treat cancer.

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ORIGINAL ARTICLES Routy, B. et al. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. *Science* **359**, 91–97 (2018) | Gopalakrishnan, V. et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. *Science* **359**, 97–103 (2018) | Matson, V. et al. The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients. *Science* **359**, 104–108 (2018)
FURTHER READING Zitvogel, L. et al. Anticancer effects of the microbiome and its products. *Nat. Rev. Microbiol.* **15**, 465–478 (2017)