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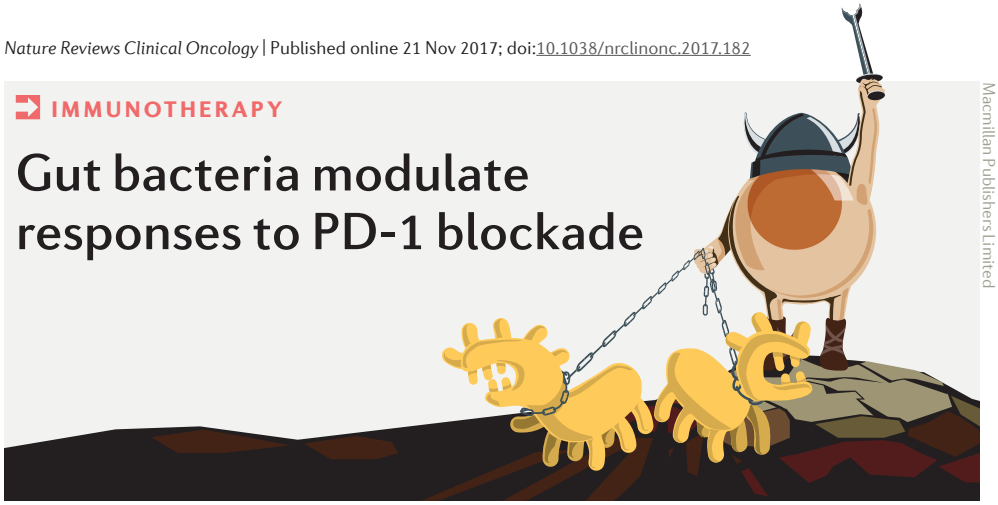
IMMUNOTHERAPY

Gut bacteria modulate responses to PD-1 blockade



For a range of cancers, anti-PD-1 or anti-PD-L1 immunotherapy has greatly improved outcomes for a minority of patients; however, predicting responses to immunotherapy remains an inexact science. Two papers published in *Science* provide new evidence indicating that the gut microbiota can influence the efficacy of PD-1 blockade.

In the first study, a group led by Laurence Zitvogel examined the effects of antibiotics on the outcomes of anti-PD-1/PD-L1 immunotherapy in patients with advanced-stage lung, kidney, or bladder cancer. Strikingly, the use of antibiotics within 2 months before or 1 month after the initiation of immunotherapy was independently associated with inferior survival outcomes. The authors hypothesize that this relationship reflects gut dysbiosis. Indeed, quantitative metagenomic analyses of the gut microbiota before and during immunotherapy revealed that, compared with non-responders, responders had enrichment of particular bacteria species, notably *Akkermansia muciniphila*, but also *Ruminococcus* spp. and others, while some were under-represented.

Causality was investigated using faecal microbiota transplantation (FMT) experiments in germ-free or antibiotic-treated mice. Importantly, syngeneic tumours in 'avatar' mice with FMT from responders were sensitive to PD-1 blockade, whereas those in avatars of non-responders were resistant. Transfer of *A. muciniphila* was found to be sufficient to instil sensitivity to immunotherapy. Immunological changes were found to be correlated with these effects, but the mechanism underlying these alterations remains unknown.

"Our research partially explains why some patients do not respond," says lead author Bertrand Routy. "Furthermore, the composition of the intestinal microbiota is a new predictive factor for success."

These conclusions are underscored by findings of the second study, from a group led by Jennifer Wargo, in which the oral and gut microbiomes of patients with metastatic melanoma were analysed. "We found that patients who responded to anti-PD-1 therapy had a higher diversity of the gut (but not oral) microbiome at baseline. Notable compositional differences also existed, with enrichment of the Ruminococcaceae family (of the Clostridiales order) in responders, and of the Bacteroidales order in non-responders," Wargo summarizes. These factors were also associated with progression-free survival, and intriguing correlations with T-cell numbers in the blood and tumour microenvironment were noted. Again, the results of FMT models confirmed the influence of the microbiota on the efficacy of PD-1 blockade.

These observations raise a number of important questions with clinical implications. First, will routine sequencing of the microbiome provide much-needed predictive biomarkers? "We need to consider this question in studies with larger cohorts across cancer types," states Wargo. "Furthermore, we will need to work together as a global community to develop standardized approaches for sample collection, processing, and analysis." Second, should factors that can modify the microbiota, including diet and probiotics, as well as medications such as antibiotics, be closely monitored in patients undergoing immunotherapy? "The provocative data from Dr Zitvogel's group demonstrate that patients who receive antibiotics just before or just after initiating immune-checkpoint blockade have worse outcomes." Finally, and potentially most importantly, can the microbiota be manipulated to enhance responses? As Wargo explains, "the microbiome can be modulated using a number of different strategies, including FMT and administration of live bacterial products or consortia of bacteria to patients; these strategies are being used in other diseases, such as inflammatory bowel disease and *Clostridium difficile* colitis." Her group and others are now working towards implementing a clinical trial incorporating modulation of the microbiota (using FMT and other strategies) into immune-checkpoint blockade in patients with cancer.

David Killock

ORIGINAL ARTICLES Routy B. *et al.* Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial cancers. *Science* http://dx.doi.org/10.1126/science.aan3706 (2017) | Gopalakrishnan, V. *et al.* Gut microbiome modulates responses to anti-PD-1 immunotherapy in melanoma patients. *Science* http://dx.doi.org/10.1126/science.aan4236 (2017)