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TUMOUR IMMUNOLOGY

Anticancer drugs need bugs

Patients who are being treated for cancer are routinely given antibiotics, as they have an increased risk of infection owing to the toxic side effects of chemotherapy. Two reports in *Science* now question the wisdom of this prophylaxis, as both studies show that an intact commensal microflora is necessary for the optimal efficacy of anticancer therapies.

Iida *et al.* compared the immune responses of antibiotic-treated and untreated mice to various transplantable tumours. They assessed gene expression in the tumour microenvironment and found that tumour-bearing mice that had been treated with antibiotics showed decreased expression of genes that are involved in inflammation, phagocytosis and adaptive immunity, and increased expression of genes that are related to tissue development, cancer and metabolism.

The authors then examined how antibiotic treatment affects the response of tumour-bearing mice to combined immunotherapy with CpG-containing oligodeoxynucleotides (CpG ODNs) — which activate Toll-like receptor 9 (TLR9) — and inhibitory antibodies that are specific for the interleukin-10 receptor (anti-IL-10R). Remarkably, treatment of mice with antibiotics impaired the ability of this immunotherapy to reduce tumour burdens and to prevent death. This effect seemed to be independent of the effects of antibiotics on the adaptive immune system but was instead due to decreased production of tumour necrosis factor (TNF) by tumour-infiltrating myeloid cells. Similar findings were obtained in tumour-bearing germ-free mice, which suggests that commensals are important for 'priming' the innate immune system to respond to immunotherapy.

By correlating faecal microbiota compositions with levels of TNF production, the authors were able to identify particular bacterial species that could promote (*Alistipes shahii*) or impair (*Lactobacillus fermentum*) the efficacy of combined immunotherapy with CpG ODNs and anti-IL-10R. Strikingly, both germ-free mice and antibiotic-treated mice also showed impaired responsiveness to oxaliplatin and cisplatin, which are chemotherapeutic agents commonly used to treat human cancers. In this case, the beneficial effect of the microbiota was independent of TNF and instead seemed to partly depend on the ability of commensals to promote the generation of reactive oxygen species by innate immune cells in the tumour microenvironment.

Viaud *et al.* began by exploring how chemotherapy affects the intestinal microbiota in mice. They found that doxorubicin and, in particular, cyclophosphamide treatment disrupted intestinal barrier function, which leads to translocation of commensal bacteria, such as *Lactobacillus johnsonii* and *Enterococcus hirae*, into the mesenteric lymph nodes and the spleen. Concomitantly, cyclophosphamide increased the frequencies of interferon-γ (IFNγ)- and IL-17-producing T cells in the spleen. This effect was dependent on the presence of the gut microbiota and signalling via the TLR adaptor MYD88, and was not seen in germ-free mice or in mice that have been treated with various antibiotics.

The authors investigated whether the bacterial species that translocate into secondary lymphoid tissues following cyclophosphamide treatment can polarize $CD4^+$ T cells into a T helper 1 (T_H1) or T_H17 cell phenotype. Indeed, they found that both *L. johnsonii* and *E. hirae* promoted T_H1 and T_H17 cell differentiation *in vitro*, as well as *in vivo* when they were orally administered to antibiotic-treated mice. Importantly, this effect of these commensals on the immune system seemed to be necessary for the antitumour efficacy of chemotherapy, as in various mouse models of cancer, tumour-bearing mice that were treated with antibiotics did not respond to cyclophosphamide therapy. Furthermore, the antitumour efficacy of cyclophosphamide could be restored in antibiotic-treated tumour-bearing mice by the adoptive transfer of $IFN\gamma^+IL\text{-}17^+$ T cells.

Taken together, these papers show that commensals can markedly affect the response to both chemotherapies and immunotherapies. They also identify a previously unappreciated risk of antibiotics in patients who receive cancer therapy.

Yvonne Bordon

> “an intact commensal microflora is necessary for the optimal efficacy of anticancer therapies”

ORIGINAL RESEARCH PAPERS Iida, N. *et al.* Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science* **342**, 967–970 (2013) | Viaud, S. *et al.* The intestinal microbiota modulates the anticancer immune effects of cyclophosphamide. *Science* **342**, 971–976 (2013)