TUMOUR MICROENVIRONMENT

Bacterial balance affects cancer treatment

Two new studies in mice have shown that disrupting the microbial balance in the gut through the use of antibiotics can affect response to cancer therapy.

Iida *et al.* specifically asked how perturbing the commensal bacteria populations in the gut by antibiotics affects tumours that are treated with immunotherapy or chemotherapy. They pretreated mice with ABX, which is a broad-spectrum antibiotic cocktail consisting of vancomycin, imipenem and neomycin, prior to inoculating the mice with subcutaneous tumours and then treating them with immunotherapy or chemotherapy.

Mice were treated with a combination immunotherapy consisting of CpG oligonucleotides, a ligand to Toll-like receptor 9 (TLR9) and inhibitory interleukin-10 receptor antibodies to activate Toll-like receptors on myeloid cells and induce tumour necrosis factor (TNF) production. Mice that were pretreated with ABX had a reduced response to this immunotherapy: there was less of an effect on tumour growth and a lower proportion of mice survived compared with mice that were not treated with ABX. The authors showed that ABX reduced TNF production: mice that lacked TNF phenocopied mice that were treated with ABX. These effects were dependent on the decreased bacterial load that was induced by ABX, as germ-free mice had a similarly attenuated response to immunotherapy. Moreover, in ABX-treated mice, TNF expression and tumour necrosis could be rescued by oral treatment with bacterial lipopolysaccharide (LPS), which is an immune cell stimulant.

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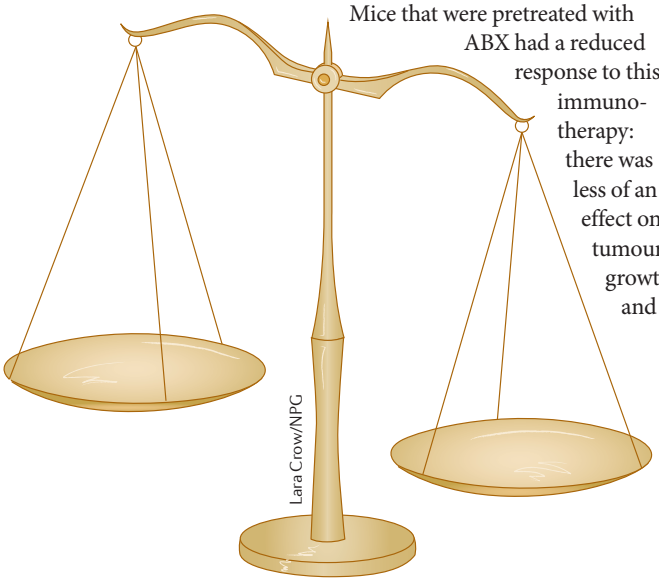

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The authors also determined the effect of the microbiota on response to therapies that do not directly affect the immune system, such as platinum-based chemotherapy. ABX-treated mice or germ-free mice that were treated with cisplatin or oxaliplatin had reduced tumour regression and survival compared with mice that were treated with cisplatin or oxaliplatin alone. The authors found that reactive oxygen species (ROS) production in tumour-infiltrating myeloid cells was required for oxaliplatin-induced tumour DNA damage and tumour regression. Accordingly, myeloid cells from ABX-treated mice produced lower levels of ROS in response to the platinum drugs. The authors further found that ROS production was dependent on NADPH oxidase 2 (encoded by *Cybb*), and in agreement with these findings *Cybb*$^{-/-}$ mice did not respond to oxaliplatin and had reduced ROS production. Moreover, mice that lacked components of the TLR pathway also had an impaired response to oxaliplatin, which suggests that gut bacteria produce TLR agonists that poise myeloid cells for ROS production in response to this drug. Thus, effective treatment with either immunotherapy or chemotherapy relies on commensal bacteria, which prime tumour-associated myeloid cells to induce TNF-dependent necrosis or ROS-dependent apoptosis, respectively, in tumours.

Viaud and colleagues investigated the effects of cyclophosphamide (CTX) on the microbiota in the intestine and how this influences the tumour immune response.

Treatment of mice with CTX led to an increased permeability of the intestine that allowed the composition of bacteria in the gut to change and also allowed selected species of Gram-positive bacteria to enter the lymph nodes and the spleen. The presence of these bacterial cells was involved in the CTX-induced conversion of naive CD4$^+$ T cells to pathogenic T helper 17 (T_H17) cells, as the eradication of the Gram-positive bacteria by ATB (a broad-spectrum antibiotic cocktail) reduced the CTX-mediated conversion of T cells. In addition, tumour-bearing mice that were treated with ATB showed reduced tumour regression in response to CTX. Interestingly, injection of pathogenic T_H17 cells into tumour-bearing antibiotic-treated mice rescued the antitumour effects of CTX. This demonstrates a causal link between the effects of CTX on gut microbiota, the accumulation of pathogenic T_H17 cells in the spleen and successful chemotherapy.

Together these studies provide insights into the effects of broad-spectrum antibiotics on the tumour microenvironment, and they have implications for the management of infection in cancer patients.

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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)