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TUMOUR MICROENVIRONMENT

That gut feeling

The gut microbiota can modulate the efficacy of anticancer therapies. Cyclophosphamide (CTX) has been shown to stimulate the translocation of selected populations of Gram-positive bacteria eliciting pathogenic T helper 17 (pT_H17) effector cell responses involved in constraining tumour growth. Now, work by Daillère and colleagues has built on these initial findings by asking which specific bacterial species in the gut can increase the antitumour immune responses of CTX and how they achieve this.

Dysbiosis of the gut with the use of broad-spectrum antibiotics (ATBs) in tumour-bearing mice is sufficient to decrease the antitumour activity of CTX. Using this same mouse model, the authors showed that oral treatment with the intestinal Gram-positive bacterium *Enterococcus hirae* was able to rescue the efficacy of CTX in tumour-bearing ATB-treated mice.

> memory T_H1 cells directed against *E. hirae* and *B. intestinihominis* was predictive of increased progression-free survival

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E. hirae translocated from the small intestine to the spleen, activating systemic pT_H17 cell responses associated with tumour antigen-specific $CD8^+$ T cells and increasing the intratumoural cytotoxic T lymphocyte (CTL)/T regulatory (T_{reg}) cell ratio. A second bacterial species, the Gram-negative *Barnesiella intestinihominis*, was also identified, as the use of colistin, an antibiotic effective against Gram-negative bacteria in tumour-bearing mice, could also reduce the antitumour activity of CTX. This commensal accumulated in the colon of CTX-treated tumour-bearing mice, inducing systemic long-term memory $CD4^+$ T helper 1 (T_H1) and a subset of $CD8^+$ T cell responses and increasing the number of tumour-infiltrating interferon-γ (IFNγ)-producing γδT cells. Interestingly, both bacterial populations decreased the numbers of T_{reg} cells in the tumour microenvironment.

In establishing which pattern recognition receptors expressed by intestinal epithelial cells could be responsible for the translocation of Gram-positive bacteria to secondary lymphoid organs, the authors observed that not only were Gram-positive bacterial translocation and *B. intestinihominis* accumulation in the colon significantly increased in nucleotide-binding oligomerization domain-containing 1 (*Nod1*) and *Nod2* double knockout (*Nod1*$^{-/-}$ *Nod2*$^{-/-}$) mice compared with wild-type (WT) mice but so too were the antitumour effects of CTX. Using single-gene knockouts, Daillère *et al.* showed that CTX-mediated control of tumour growth was improved in *Nod2*$^{-/-}$ mice compared with WT mice whereas it was not in *Nod1*$^{-/-}$ mice, suggesting that the NOD2 receptor acts as an immune sensor keeping the immunogenicity of *E. hirae* and *B. intestinihominis* in check. Confirming the role of NOD2, conditional *Nod2* deletion in the intestinal epithelial cells of mice led to accumulation of *E. hirae*, pT_H17 cells and γδT cells in the spleen following CTX treatment. Furthermore, *E. hirae* and *B. intestinihominis* could induce apoptosis of intestinal epithelial cells in 3D small intestine organoids generated from *Nod2*$^{-/-}$ intestinal stem cells, suggesting that in conditions of NOD2 deficiency *in vivo* this could be a mechanism by which bacterial species translocate and elicit tumour immunosurveillance.

Lastly, the authors analysed T cell responses in the blood of 38 patients with advanced lung or ovarian cancer treated with platinum-based chemotherapy. This revealed that the presence of memory T_H1 cells directed against *E. hirae* and *B. intestinihominis* was predictive of increased progression-free survival.

This study provides further evidence that immunogenic gut microbial communities should now be considered yet another tumour microenvironmental factor determining therapeutic outcome. It also provides a paradigm for implementing a new treatment design whereby supplementing existing anticancer drugs with selected gut bacteria could improve the efficacy of chemotherapy under regimens of ATBs or following tumour-mediated changes in the composition of the gut microbiota.

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ORIGINAL ARTICLE Daillère, R. *et al.* *Enterococcus hirae* and *Barnesiella intestinihominis* facilitate cyclophosphamide-induced therapeutic immunomodulatory effects. *Immunity* **45**, 931–943 (2016)