was independent of systemic markers of inflammation and of disease severity and duration.

The authors were also able to define a ligand–receptor activity network that probably drives the GIMATS module. In addition, bulk RNA sequencing (that is, composite mRNA estimates from many different cells measured together) in four large cohorts of patients with Crohn's disease confirmed the existence of the GIMATS module. Notably, in a paediatric inception cohort, a high GIMATS score at baseline was associated with non-response to anti-TNF therapy.

The authors expect that future multi-parameter immunofluorescence studies will precisely identify the critical cell–cell interactions that drive inflammatory activation in Crohn's disease. Such findings could help in the development of alternative treatment options for patients with treatment-resistant disease.

Isobel Leake

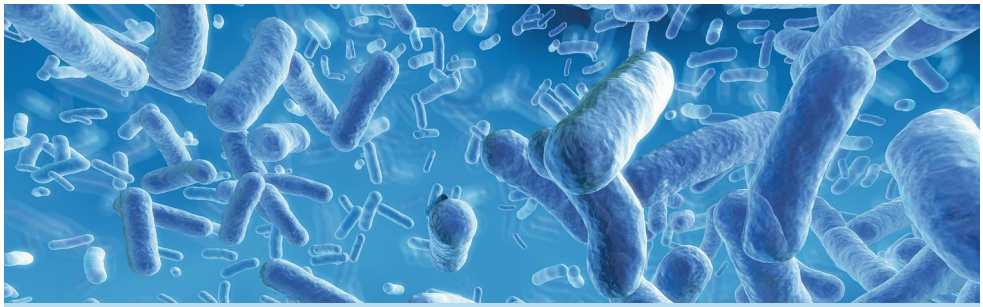
ORIGINAL ARTICLE Martin, J. C. et al. Single-cell analysis of Crohn's disease lesions identifies a pathogenic cellular module associated with resistance to anti-TNF therapy. *Cell* **178**, 1493–1508.e20 (2019)

to be a major environmental entraining signal for ILC3s as circadian oscillations were maintained in ILC3s despite constant darkness. Finally, deregulation of brain rhythmicity (either surgically or genetically induced targeting of the suprachiasmatic nuclei in the hypothalamus, a main integrator of light signals) disrupted circadian ILC3 oscillations and led to altered lipid metabolism and body composition (increased fat accumulation) and deregulation of the gut microbiota in mice.

"We have shown that light cues and brain-derived circadian signals regulate enteric ILC3s and intestinal homeostasis," notes Veiga-Fernandes, who now aims to explore the molecular, cellular and circuitry aspects of neuroimmune interactions in different tissues. "This is a major challenge that will allow us to uncover whether therapeutic targeting of these neuroimmune axes can be explored in inflammatory and metabolic diseases," he adds.

Katrina Ray

ORIGINAL ARTICLE Godinho-Silva, C. et al. Light-entrained and brain-tuned circadian circuits regulate ILC3s and gut homeostasis. *Nature* https://doi.org/10.1038/s41586-019-1579-3 (2019)



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PANCREATIC CANCER

Tumour microbiome defines outcomes

Determinants of long-term outcomes have remained elusive in pancreatic ductal adenocarcinoma (PDAC), a disease with a 5-year overall survival (OS) of only 9%. Now, a new study reports that the intratumoural microbiome defines outcomes.

To investigate associations between microbiome composition and outcomes, 16S ribosomal RNA gene sequencing was performed on resected PDAC tumours from patients with long-term survival (LTS; OS >5 years) and short-term survival (STS; OS <5 years). Tumour microbial diversity was markedly higher in LTS patients, and patients with high diversity survived longer than those with low diversity (median OS 9.66 versus 1.66 years; $P = 0.00016$), indicating the potential influence of microbiome composition on progression.

High-dimensional comparisons revealed major differences in tumour microbial communities at various taxonomic levels. Importantly, although no predominant genus was present in the STS tumours, LTS tumours were enriched for genera *Pseudoxanthomonas*, *Saccharopolyspora* and *Streptomyces*, and patients with high abundance of these three genera had markedly prolonged OS. Area under curve analyses revealed that, when combined with *Bacillus clausii*, a species enriched in LTS tumours, the three-genus intratumoural microbiome signature was highly predictive of long-term survivorship.

Following the hypothesis that intratumoural bacteria shape the immune microenvironment, Riquelme et al. next assessed immune infiltration. Using an immunostaining approach, LTS tumours were shown to have greater $CD3^+$ and $CD8^+$ T cell and granzyme B^+ cell numbers than STS tumours, with no major differences in numbers of regulatory T cells, macrophages or myeloid-derived suppressor cells (MDSCs). Among all patients, positive correlations were noted between OS and $CD3^+$, $CD8^+$ and granzyme B^+ tissue densities, between $CD8^+$ and granzyme B^+ tissue densities and microbial diversity, and between $CD8^+$ tissue density and the three-genus signature, suggesting that the tumour microbiome drives antitumour immune responses through $CD8^+$ T cell recruitment and activation.

Strikingly, analysis of taxonomic composition in stool samples, tumour specimens and normal tissues from three patients with PDAC revealed that the gut microbiome represents ~25% of the human tumour microbiome, indicative of gut–tumour microbiome crosstalk. To test the hypothesis that the gut microbiome modulates the intratumoural microbiome, the authors transplanted stool samples from STS patients with advanced PDAC into mice harbouring orthotopic syngeneic tumours. After faecal microbiota transplantation (FMT), ~40% of human donor stool bacteria were present in the recipient mouse gut microbiome and a small proportion (~5%) of the mouse tumour microbiome originated from human donors.

To assess the effect of microbiome modulation on tumour growth, human-to-mouse FMT was performed using stool samples from STS and LTS patients and healthy donors. Importantly, mice receiving LTS-FMT had markedly reduced tumour growth relative to mice receiving STS-FMT or healthy-donor FMT, suggesting that LTS bacteria exert antitumour effects. Indeed, this differential effect was attenuated when mice were treated with antibiotics after FMT. Furthermore, flow cytometry analyses revealed enrichment for $CD8^+$ and activated T cell infiltration in LTS-FMT tumours and for immunosuppressive regulatory T cells and MDSCs in STS-FMT tumours, and antibody-mediated depletion of $CD8^+$ T cells abrogated the antitumour effect induced by LTS-FMT, establishing a protective role for this immune population.

Overall, the study unravels intratumoural microbial events associated with prolonged survival in PDAC and illustrates that intratumoural microbiome composition, which is influenced by gut–tumour microbial crosstalk, influences the host immune response and natural history.

"We plan to conduct a pilot trial to determine if altering the gut microbiome can affect the tumour microbiome and immunosuppressive microenvironment characteristic of pancreatic cancer," concludes lead author Florencia McAllister.

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ORIGINAL ARTICLE Riquelme, E. et al. Tumor microbiome diversity and composition influence pancreatic cancer outcomes. *Cell* **178**, 795–806.e12 (2019)