(HSPCs) of various *Trp53* genotypes, *Trp53*$^{missense/-}$ HSCPs had a relative competitive fitness advantage over *Trp53*$^{+/-}$ HSPCs upon DNA damage. No relative competitive difference was observed between *Trp53*$^{missense/-}$ and *Trp53*$^{-/-}$ HSPCs. Instead of a transcriptional GOF, these data support a DNE of missense mutant p53, in which the missense variant inhibits transcriptional activity of the wild-type protein, thereby driving clonal selection.

Finally, in a cohort of 164 patients with *TP53*-mutant AML, the majority had missense mutations located in the DNA-binding region. These patients did not have more aggressive disease than those with truncating mutations, supporting the notion that a mutant-p53-mediated DNE initially drives selection of *TP53*-mutant clones, and that a loss of wild-type p53 function determines poor outcome in these patients.

Ulrike Harjes

ORIGINAL ARTICLE Boettcher, S. et al. A dominant-negative effect drives selection of TP53 missense mutations in myeloid malignancies. *Science* **365**, 599–604 (2019)

of chemical modifications were made to both entities. The capacity of phage-guided nanoparticles to control tumour growth was then tested in orthotopic mouse models and *Apc*$^{Min/+}$ mice. Sequential oral or intravenous administration of the modified phages and the drug-loaded DNPs, 24 hours after gavage with *F. nucleatum* to mimic cancer-associated bacterial expansion, resulted in increased accumulation in the tumour and improved therapeutic performance of DNPs over the monotherapy irinotecan as well as reduced side effects associated with systemic chemotherapy.

The hope is that this phage-guided nanotechnology could be tailored to deliver different drugs and modulate other microbial species in a diverse range of cancer types.

Anna Dart

ORIGINAL ARTICLE Zheng, D.-W. et al. Phage-guided modulation of the gut microbiota of mouse models of colorectal cancer augments their responses to chemotherapy. *Nat. Biomed. Eng.* https://doi.org/10.1038/s41551-019-0423-2 (2019)
RELATED ARTICLE Elinav, E. et al. The cancer microbiome. *Nat. Rev. Cancer* **19**, 371–376 (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.

Conor A. Bradley

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