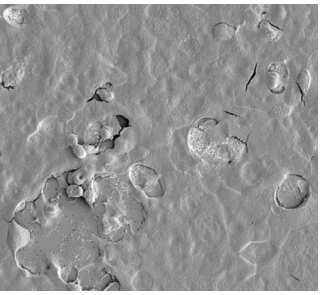


Credit: Scanning electron microscopy image of intestinal epithelium cultured with pore-forming *K. pneumoniae*. Image reproduced from Nakamoto, N. et al. *Nat. Microbiol.* https://doi.org/10.1038/s41564-018-0333-1 (2019).

microbiota interact with the intestinal epithelial barrier," says Nakamoto. The addition of PSC-associated *K. pneumoniae* was found to induce the formation of epithelial pores in the monolayer through contact-dependent apoptosis. This effect correlated with bacterial translocation and subsequent T_H17-mediated hepatobiliary injury in mice. Furthermore, antibiotic treatment ameliorated the T_H17 immune response.

"The finding that antibiotics targeting *K. pneumoniae* reduced T_H17 responses suggests that disease-specific bacteria might serve as a potential therapeutic target for PSC," concludes Nakamoto. "We still need to validate the presence of pore-forming *K. pneumoniae* using a larger cohort and we are planning a future project to eliminate these bacteria in a specific way," he adds.

Iain Dickson

ORIGINAL ARTICLE Nakamoto, N. et al. Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis. *Nat. Microbiol.* https://doi.org/10.1038/s41564-018-0333-1 (2019)

> "…blocking of GLUL improved phagocytic capacity in induced and patient-derived ACLF monocytes"

monocytes showed glycolytic enzyme downregulation, similar to M2 macrophages, in which enhanced glutamine anabolism has also been observed. In patient-derived ACLF monocytes, GLUL expression was increased and glutaminase (GLS) expression was decreased. GLUL:GLS ratios of ACLF monocytes positively correlated with disease severity scores, indicating the biological relevance of this finding. Notably, pharmacological blocking of GLUL improved phagocytic capacity in induced and patient-derived ACLF monocytes. "…this work highlights the importance of metabolic immunotherapeutic strategies in the treatment of ACLF," write the authors.

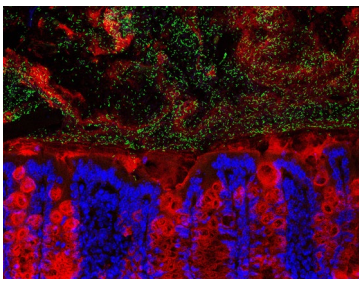
Clemens Thoma

ORIGINAL ARTICLE Korf, H. et al. Inhibition of glutamine synthetase in monocytes from patients with acute-on-chronic liver failure resuscitates their antibacterial and inflammatory capacity. *Gut* https://doi.org/10.1136/gutjnl-2018-316888 (2018)
FURTHER READING Sarin, S. K. et al. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat. Rev. Gastroenterol. Hepatol.* **13**, 131–149 (2016)

GUT MICROBIOTA

Bacterial strains modulate CD8$^+$ T cell function and cancer immunity

Specific gut microbial strains isolated from human faeces induce cytotoxic CD8$^+$ T cells and promote immunity against cancer and intracellular pathogens, according to new findings published in *Nature*.



Credit: The antitumour effects of anti-PD1 treatment were substantially greater in the groups that received 11-mix. Image courtesy of Iori Motoo, RIKEN Center for Integrative Medical Sciences, Japan

In the past few years, the gut microbiota has been recognized as an important factor in intestinal CD4$^+$ T cell maturation, and specific commensal bacteria have been identified that drive regulatory T cells and T helper 17 cell development. However, little is known about the role of gut microorganisms in the development of cytotoxic CD8$^+$ T cells, which protect against intracellular pathogens and have an important role in cancer immunity.

In a new study, Tanoue and colleagues focused on how the gut microbiota alters the abundance and function of cytotoxic CD8$^+$ T cells, identified by IFNγ positivity. In initial work, the authors found that these cells were present in the intestinal lamina propria in normally housed mice, but were less abundant in mice given antibiotics and absent in germ-free (GF) mice. To identify clinically relevant specific bacterial strains able to induce the development of cytotoxic CD8$^+$ T cells, the team administered human faecal samples from 6 healthy donors to GF mice. Analysis of the caecal microbiota of these mice ultimately revealed 11 strains — 7 Bacteroidales and 4 non-Bacteroidales, present in the human gut microbiota in low abundance — associated with intestinal cytotoxic CD8$^+$ T cell induction. These results were confirmed by inoculating another group of GF mice with this 11-strain mix (11-mix). Using a variety of knockout mice, the researchers found that the T cell induction effect of 11-mix was dependent on CD103$^+$ dendritic cells via MHC class Ia.

Tanoue and colleagues then explored whether the 11 strains could improve host immunity against an orally administered pathogen. Administration of 11-mix to GF or specific-pathogen-free (SPF) mice improved clearance of *Listeria monocytogenes* and reduced infection severity compared with no active treatment. These positive effects were abrogated when CD8$^+$ T cells were depleted.

To assess whether 11-mix also altered antitumour immunity, the investigators engrafted cancer cells into GF and SPF mice and treated them with combinations of 11-mix, anti-PD1 therapy or control agents. The antitumour effects of anti-PD1 treatment were substantially greater in the groups that received 11-mix than the groups receiving the control treatment — this effectiveness was abolished when cytotoxic CD8$^+$ T cells were ablated. In addition, no histological evidence of potentially treatment-limiting colitis associated with anti-PD1 therapy was seen in mice that received 11-mix. Finally, 11-mix suppressed tumour growth even in the absence of anti-PD1 therapy.

"Our isolated strains have great biotherapeutic potential and could be broadly applicable to enhancing the treatment of cancer and infectious disease alike," write the authors. Future work will clarify the mechanisms involved and the applicability of these findings to human disease.

Hugh Thomas

ORIGINAL ARTICLE Tanoue, T. et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* **565**, 600–605 (2019)
FURTHER READING Alexander, J. L. et al. Gut microbiota modulation of chemotherapy efficacy and toxicity. *Nat. Rev. Gastroenterol. Hepatol.* **14**, 356–365 (2017)