

Organoids demonstrate gut infection by SARS-CoV-2

A new study published in *Science* has used human small intestinal organoids (hSIOs) to support clinical evidence that suggests severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect and replicate in the intestinal epithelium.

Although respiratory symptoms dominate the clinical presentation of coronavirus disease 2019, many reports exist of gastrointestinal symptoms in some patients, leading to speculation that the intestine might represent a viral target organ. Indeed, peak expression of the SARS-CoV-2 receptor, ACE2, is thought to occur in intestinal enterocytes.

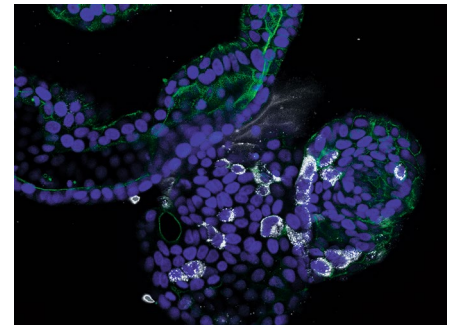
“The Clevers lab has been optimizing hSIO cultures and their differentiation into all mature lineages,” explains author Joep Beumer. “We had already identified the best conditions to achieve high ACE2-expressing enterocytes in culture. Therefore, we set out on this collaborative effort to use organoids to show that SARS-CoV-2 viral replication can occur in these cells.”

The investigators used hSIOs derived from primary gut epithelial stem cells, which

were exposed to SARS-CoV-2 under different conditions. “To determine which cells were infected, we visualized viral antigens and host lineage markers using confocal microscopy. Infection at an ultrastructural level could be followed using transmission electron microscopy,” says Beumer.

This approach showed that enterocytes were readily infected by SARS-CoV-2 with substantial titres of infectious viral particles detected in all conditions tested. “These experiments proved that SARS-CoV-2 can productively infect cells of the intestinal epithelium,” says Beumer, but whether this finding has a role in SARS-CoV-2 transmission needs further investigation. The team also sequenced mRNA to examine the host response to the virus, finding that infection induced upregulation of genes attributed to antiviral type I and III interferon responses.

“Our goal is to set up relevant models to improve our fundamental understanding of coronaviruses, which could lead to the rational design of antiviral therapies,” concludes Beumer. “We also plan to construct



Credit: Confocal microscopy image of a human intestinal organoid 60 h following infection with SARS-CoV-2. Actin filaments are stained green, nuclei are blue and the virus is white. Image courtesy of J. Beumer.

a biobank of genetically modified organoids using CRISPR-Cas9 that we hope could aid in the understanding of viral entry and the epithelial response to it.”

These findings were confirmed in a second study published in *Nature Medicine*. This study also provided evidence of active SARS-CoV-2 replication in human intestinal organoids, as well as upregulation of type III interferon responses.

Iain Dickson

ORIGINAL ARTICLE Lamers, M. M. et al. SARS-CoV-2 productively infects human gut enterocytes. *Science* <https://doi.org/10.1126/science.abc1669> (2020)

RELATED ARTICLE Zhou, J. et al. Infection of bat and human intestinal organoids by SARS-CoV-2. *Nat. Med.* <https://doi.org/10.1038/s41591-020-0912-6> (2020)

Microbiota modulates aspirin chemoprevention in CRC

Aspirin reduces the development of colorectal tumours in mouse models, an effect that is dependent on the gut microbiota. Moreover, the gut microbiota altered the bioavailability and chemopreventive effects of aspirin in mice, according to new research.

Evidence indicates that aspirin has chemopreventive benefit in human colorectal cancer (CRC), but the reported overall efficacy has varied. As the gut microbiota seems to have a role in CRC development and in drug metabolism, Jun Yu and colleagues wanted to explore this relationship in mouse models of CRC. “As accumulating evidence suggest that drugs shift the composition of gut microbiota, [and] conversely, gut microbiota affects the drug’s metabolism, we aimed to elucidate the specific role of the gut microbiota in aspirin-based CRC chemoprevention in various mouse models,” Yu explains.

“the gut microbiota altered the bioavailability and chemopreventive effects of aspirin in mice”

The researchers examined the effects of gut microbiota depletion (via antibiotics) on the preventive efficacy of aspirin in two different mouse models of CRC (mimicking human CRC associated with either familial adenomatous polyposis or inflammatory bowel disease). Crucially, aspirin administration reduced colorectal tumour burden in both models of CRC, but only in mice with a depleted gut microbiota and not in mice with an intact microbiota. The same trend for fewer colorectal tumours was observed in germ-free mice given aspirin versus conventionalized germ-free mice given aspirin.

Notably, plasma levels of aspirin were higher in microbiota-depleted mice than in mice with an intact gut microbiota; a concomitant decrease in cyclooxygenase 2 and prostaglandin 2 (factors thought to be involved in the

chemopreventive effects of aspirin) was observed in microbiota-depleted mice. Interestingly, analysis of the luminal contents from the mice demonstrated that aerobic gut microorganisms degraded aspirin, with *Lysinibacillus sphaericus* identified as one such microorganism that degraded aspirin in vitro and in vivo. Finally, monocolonization of germ-free mice with *L. sphaericus* decreased plasma levels of aspirin and, in CRC mouse models, *L. sphaericus* impaired the chemopreventive efficacy of aspirin.

“The specific mechanism through which *L. sphaericus* degrades aspirin is still unknown,” explains Yu, who plans further work to determine the enzymes generated from *L. sphaericus* that catalyse aspirin degradation. “Human study is essential to evaluate the impact of *L. sphaericus* on aspirin-based CRC chemoprevention,” she adds.

Katrina Ray

ORIGINAL ARTICLE Zhao, R. et al. Aspirin reduces colorectal tumor development in mice and gut microbes reduce its bioavailability and chemopreventive effects. *Gastroenterology* <https://doi.org/10.1053/j.gastro.2020.05.004> (2020)