What's in a stomach?

As models of human tissues go, organoids—small three-dimensional structures derived from stem cells or differentiated cells—have shown particular promise in recent years. Human organoids resembling the intestine, prostate and other tissues have been developed and used to study cancer-causing mutations and potential therapeutics. Now, Wells, Zavros and colleagues report the generation of human gastric organoids that resemble stomach tissue and support *Helicobacter pylori* infection[1].

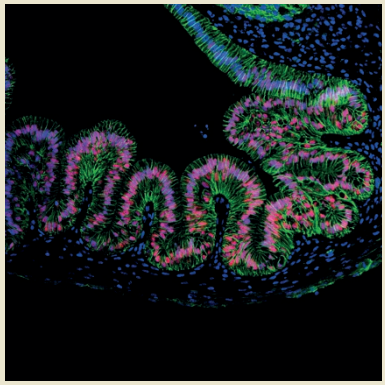
To make the organoids, the scientists first identified the factors that mediate embryonic development of the stomach and then recapitulated the process in a dish. They started by differentiating human induced pluripotent stem cells into endoderm, from which gut tissues are derived. Then, drawing on their previous work and the work of others, largely based on studies of mouse development, they tested multiple culture conditions to guide the cells to form foregut. Because foregut also gives rise to other tissues such as pancreas, they then needed to direct differentiation to one of the domains of the stomach: the fundus, where peptidases and acid are produced, or the antrum, which contains mucus- and hormone-producing cells. Using additional differentiation factors and culturing the cells in a semisolid matrix proved successful. The researchers obtained organoids that have a complex epithelium and a marked resemblance to human antrum.

The human gastric organoids generated by Wells, Zavros and colleagues contain mucus, endocrine, epithelial and LRG5-expressing stem cells. The factors and conditions that drove generation of the organoids closely mimicked what is known about embryonic development of the stomach in mice.

"This is a clever and methodological approach that uses the principles of developmental biology for tissue engineering," says Ramesh Shivdasani of the Dana-Farber Cancer Institute and Harvard Medical School, who was not involved in the study. Although it is not clear whether these factors—and these concentrations—act in the same way during human development, the approach shows that "the broader mechanisms that drive gastric development are likely to be conserved between mouse and human, and that when you take a lesson from the mouse and apply it to the human setting, it works," he says.

Organoids are a promising resource to reconstruct human disease. They have tissue complexity, which cell lines lack, are a renewable resource (unlike biopsy samples), and can model aspects of human tissues that tissues from other species cannot. To demonstrate the potential use of human gastric organoids as a model of the stomach mucosa, the researchers inoculated the lumen of the organoids with *H. pylori*, a bacterial pathogen that infects the stomach and causes disease, often leading to gastric cancer. *H. pylori* associated tightly with organoid cells and delivered CagA, a virulence factor, to the organoid epithelium[1].

Most strains of *H. pylori* do not infect rodents, says Karen Ottemann of the University of California, Santa Cruz, highlighting the need



for human gastric models to study the disease. "It is an open question, but a lot of the disease caused by *H. pylori* is thought to be due to inflammation," says Ottemann, who collaborates with the authors but was not part of this study. Although this system could be used to dissect how much of the disease is not due to inflammation, she says, "a great next step would be to include immune cells in the organoids." Because major gene regulatory pathways in *H. pylori* are induced by acid in the stomach, development of human gastric organoids that resemble the fundus would likely also be welcomed by investigators. Human antral organoids will give them plenty to work with in the meantime.

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1. McCracken, K.W. *et al. Nature* 10.1038/nature13863 (29 October 2014).