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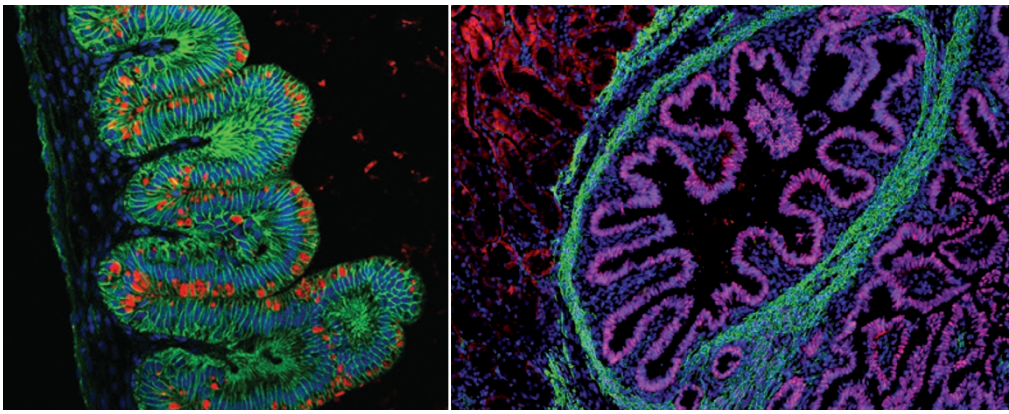
REGENERATIVE MEDICINE

Modelling the gastrointestinal tract—grow your own gut and stomach?

Complex, 3D tissue structures that can be used as models of the gastrointestinal tract have been developed by directing the differentiation of induced pluripotent stem cells (PSCs). In two new studies, investigators have developed PSC-derived human gastric tissue (gastric organoid) *in vitro* and a PSC-derived *in vivo* model of the human small intestine, respectively. Such models could be used to further understand the physiology of the gastrointestinal tract in health and disease.

Previous work has demonstrated that human PSCs can be differentiated *in vitro* into intestinal tissue (specifically hindgut), but thus far gastric tissue and foregut morphogenesis (from which the stomach derives) has not been shown. "Given the prevalence of gastric diseases such as peptic ulcers and gastric cancer, and the lack of human models, we decided to use a similar approach in attempts to generate human gastric tissues *in vitro*," explains author James Wells, whose team focused on the generation of human antral tissue.

In the first study published in *Nature*, the researchers generated human gastric organoids ~2–4 mm in diameter over the course of 3–4 weeks by temporal manipulation of several growth factors and pathways (including FGF, WNT, BMP, retinoic acid and EGF signalling) to direct PSC differentiation. Strikingly, the development and growth of these human gastric organoids paralleled stomach development *in vivo*, being found to be nearly identical to the antrum of a mouse stomach. Primitive gastric pit and gland domains, proliferative zones, mucous cells and endocrine cells (positive for gastrin, ghrelin, somatostatin and serotonin) were present. In addition, the gastric organoids could be infected with *Helicobacter pylori*. The bacteria were tightly associated with the organoid epithelium within 24 h of microinjection into the lumen of the epithelium, with the virulence factor CagA translocating into the organoid epithelial cells as expected.



PSC-derived gastric tissue (left; 2014 Macmillan Publishers Limited © McCracken, K. W. *et al. Nature* doi:10.1038/nature13863) and intestinal tissue (right; courtesy of M. A. Helmrath).

"The organoid culture model represents a significant advance in our ability to replicate the gastric environment *in vitro* and thus provides an innovative, unique and translational approach to study changes in gastric epithelial cells in relation to the direct interaction with *H. pylori*," notes co-author Yana Zavros.

Although PSC-derived intestinal tissue has already been demonstrated *in vitro*, these human intestinal organoids (HIOs) are thought to represent only the early stages of development. In the second study, published in *Nature Medicine*, the researchers generated HIOs *in vitro* from both human embryonic stem cells and induced PSCs that can engraft *in vivo* when transplanted under the kidney capsule in mice—forming a functional model of the human small intestine with mature, fully differentiated intestinal tissue. "We hypothesized that transplantation would differentiate the cells and were amazed when they actually formed fully laminated human intestinal tissues," says author Michael Helmrath.

The differentiation process for HIOs took ~35 days *in vitro*, with a further 6 weeks for maturation once transplanted *in vivo*; at the time of harvest, these HIOs had grown 50–100 times larger in volume, with 92.4% of transplanted HIOs having successfully engrafted under the kidney capsule. Marked expansion and maturation of the intestinal epithelium and mesenchyme (including production of brush border enzymes and visible subepithelial and smooth muscle layers) was observed. Crucially, the transplanted intestinal tissue had digestive functions (as confirmed by permeability and peptide uptake studies) and also responded to humoral factors after ileocaecal resection in the mice.

"We now have the ability to make functional human intestine from patient-specific single cells that is able to absorb, digest and respond to circulating factors," notes Helmrath, who hopes that one day this approach could be adapted for regenerative medicine. Future studies should confirm whether both these new model systems can be used in drug development or to further understanding of the pathogenesis of gastrointestinal disease.

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Original articles McCracken, K. W. *et al.* Modelling human development and disease in pluripotent stem-cell-derived gastric organoids. *Nature* doi:10.1038/nature13863 | Watson, C. L. *et al.* An *in vivo* model of human small intestine using pluripotent stem cells. *Nat. Med.* doi:10.1038/nm.3737