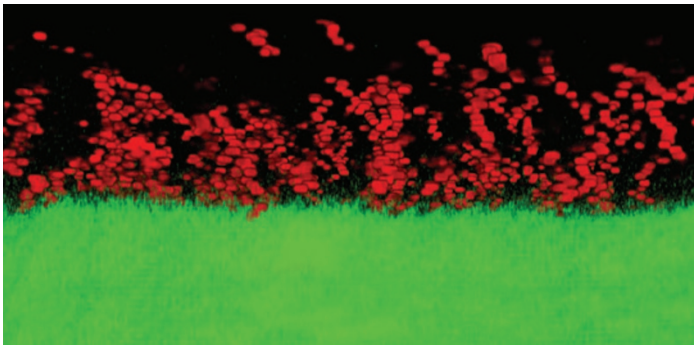
Nature Reviews Gastroenterology & Hepatology **11**, 516 (2014); published online 29 July 2014; doi:10.1038/nrgastro.2014.140

INTESTINAL TRACT

Patient-derived intestinal spheroids—culturing the gut



Courtesy of K. L. VanDussen

Researchers have developed a new cell-culture system whereby human gastrointestinal epithelial cell lines can be rapidly generated (within weeks) from patient biopsy samples. This system could prove useful for individualized medicine, potentially enabling functional *in vitro* assays for individual patients to be performed.

In their new study, Matthew Ciorba, Thaddeus Stappenbeck and colleagues from the Washington University School of Medicine adapted a protocol originally developed for the generation of mouse intestinal epithelial cells. Intestinal crypts were isolated from human biopsy samples taken during routine endoscopy of the upper and lower gastrointestinal tract. These crypts were then cultured in a medium containing critical growth factors (Wnt3a, R-spondin and Noggin) to enable the expansion of proliferative stem and progenitor cells. In doing so, small intestinal epithelial spheroids formed.

In total, 65 different human spheroid cell lines were established from a wide array of regions along the gastrointestinal tract, and from both healthy individuals and those with inflammatory disease (GERD or IBD). Robust growth was observed for these cultured intestinal spheroids, which seemed to retain a region-specific differentiation programme. "We found that the human cell lines retained memory of the tissue site from which they originated; for example, upon differentiation, cultured cells originating from small intestine biopsies expressed gene markers specific to this region *in vivo*, but not colon-specific markers," explain Ciorba and Stappenbeck.

A functional, polarised epithelial cell monolayer could be formed from the intestinal spheroids, which was covered in a mucus layer. Furthermore, novel adherence phenotypes of several different strains of pathogenic *Escherichia coli* (enteroaggregative, enteropathogenic and enterohaemorrhagic strains) were observed with respect to ileal and rectal epithelial cells.

"The rapid generation of human gastrointestinal epithelial cell cultures that can be grown as monolayers with the luminal surface exposed ... mimics the normal intestine in which there is direct access to the apical surface for drugs taken orally and for many pathogens that are exposed to the luminal surface of the gastrointestinal tract," notes Mark Donowitz (Johns Hopkins University School of Medicine), who was not involved in the study. Although a step forward in the field, he notes that more studies are needed to determine how closely this system mimics the normal, healthy intestine in terms of transport or digestive function.

Although more work is needed to reproduce and validate this work, the study authors are hopeful and are planning further research to investigate region-specific and cell-type-specific functions of intestinal epithelial cells in health and disease. "In many ways, this technique will allow us to explore how we might take a personalized approach to the understanding, diagnosis and, eventually, treatment of a specific individual's gastrointestinal disease," they conclude.

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Original article VanDussen, K. L. *et al.* Development of an enhanced human gastrointestinal epithelial system to facilitate patient-based assays. *Gut* doi:10.1136/gutjnl-2013-306651