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EDITORIAL

Move Over Caco-2 Cells: Human-Induced Organoids Meet Gut-on-a-Chip

The intestinal epithelium serves as both a crucial barrier and a critical site of interaction between the body and the environment. As such, it comprises a large surface area, and is implicated in a wide range of diseases including inflammatory bowel disease, celiac disease, infectious diarrheas, and intestinal cancers. Architecturally, the small intestine is notable for its proliferative crypts, where stem and transit-amplifying progenitor cells reside, and villi, which consist of multiple differentiated cell types from the absorptive and secretory lineages, including enterocytes, goblet cells, Paneth cells, tuft cells, M cells, and enteroendocrine cells. The polarized epithelial monolayer is supported by a network of mesenchymal and immune cells residing beneath the basement membrane, which play an important, but poorly defined, role in establishing, maintaining, and regulating intestinal morphology.

Until recently, the study of the intestinal epithelium has been limited to working with transformed intestinal cancer cell lines, such as Caco2 cells. Despite their myriad advantages, such cells fail to recapitulate the normal physiology and lineage development of the native intestinal epithelium. With the advent of intestinal organoid technology in 2009, it became possible to culture primary mouse and human intestinal epithelium as 3-dimensional organotypic miniguts in a Matrigel (Corning, Tewskbury, MA) matrix that reliably recapitulates intestinal epithelial biology. Although the ability to culture organoids has enabled enormous progress in the field, the 3-dimensional nature of these structures presents certain challenges, including difficulties with imaging, accessing the central lumen, and co-culturing with other cell types. Subsequent innovations led to organoid-derived monolayer cultures, which have begun to address a number of these challenges. An additional advance arose with the development of gut-on-a-chip technology, whereby cellular monolayers can be maintained in engineered microenvironments that allow for the addition of separate luminal and basolateral compartments, the regulation of biomimetic parameters such as flow rate and mechanical stretch, and interactions between separate organ systems. Although promising, to date, gut-on-a-chip technology has yet to be studied with primary cells, limiting its scientific and commercial applications.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Workman et al[1] showed that human intestinal organoids (HIOs), derived from induced pluripotent stem cells, can be incorporated successfully into gut-on-a-chip technology. Although more complicated to generate than epithelial-only organoids isolated from intestinal biopsy specimens, HIOs have the advantage of allowing for the generation of multiple other immune cell types (macrophages, dendritic cells, neutrophils) from the same individual. Workman et al[1] first studied the impact of co-culturing epithelial and mesenchymal cells because HIOs contain both, but discovered that the presence of mesenchymal cells significantly abrogated the expansion of an epithelial monolayer within the chip. To overcome this issue, they used flow cytometry to specifically sort for epithelial cells only using an antibody to E-Cadherin, which produced more efficient monolayers. This finding is particularly interesting given the recent report from Kasendra et al utilizing epithelium from biopsy-derived human organoids, which noted increased efficiency of monolayer formation when human intestinal microvascular endothelial cells were added to the lower chamber of the chip.[2] The role of non-epithelial cells in gut-on-a-chip technology therefore requires further investigation. Further analysis showed a polarized monolayer with a brush border and differentiated cells expressing markers for goblet cells, Paneth cells, enterocytes, and enteroendocrine cells, albeit in low numbers. The paucity of differentiated cells was perhaps unsurprising given the relatively high number (~50%) of actively cycling cells, suggesting an abundance of stem and/or transit-amplifying cells. Importantly, they showed that the addition of continuous luminal flow in the context of adequate cell density led to the development of villus-like projections, adding to the overall utility of the chip model for the study of normal intestinal morphology. Finally, they showed that the chip monolayers were biologically responsive to classic stimuli that are relevant to intestinal disease such as inflammatory cytokines, key drivers of inflammatory bowel disease pathophysiology. For example, compared with Caco2 chip-derived monolayers, the HIO chip-derived monolayers showed a significant induction in interferon-γ downstream gene targets, suggesting that the HIO model more closely models the normal and pathophysiologic responses of the intestinal epithelium.

In summary, Workman et al[1] have elegantly shown the feasibility of using human intestinal organoids to create a gut-on-a-chip. The extension of this technology to primary human cells opens the door to a variety of scientific and commercial avenues of inquiry including drug discovery and personalized medicine. For example, the human gut-on-a-chip could be linked with other organs on a chip (eg, lung, liver) to better model multisystem conditions such as sepsis, multisystem organ failure, or systemic drug toxicity. In

addition, the tunable microenvironment allows for the modulation of flow and mechanical stretch as well as the ability to separately adjust the culture conditions in the luminal or basolateral channels. Finally, the chip monolayer approach may facilitate the incorporation of other relevant cell types such as microbes, mesenchymal cells, and immune cells, and, as such, will bring the field even closer to a tractable experimental system that faithfully recapitulates human intestinal epithelial physiology.

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Conflicts of interest
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