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REVIEW

Gastrointestinal Organoids: Understanding the Molecular Basis of the Host–Microbe Interface

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SUMMARY

New methods enable prolonged culture of human intestinal tissue in the laboratory. This review summarizes the use of these tools in the study of host–microbe interactions and suggests future avenues of research.

In recent years, increasing attention has been devoted to the concept that microorganisms play an integral role in human physiology and pathophysiology. Despite this, the molecular basis of host–pathogen and host–symbiont interactions in the human intestine remains poorly understood owing to the limited availability of human tissue, and the biological complexity of host–microbe interactions. Over the past decade, technological advances have enabled long-term culture of organotypic intestinal tissue derived from human subjects and from human pluripotent stem cells, and these in vitro culture systems already have shown the potential to inform our understanding significantly of host-microbe interactions. Gastrointestinal organoids represent a substantial advance in structural and functional complexity over traditional in vitro cell culture models of the human gastrointestinal epithelium while retaining much of the genetic and molecular tractability that makes in vitro experimentation so appealing. The opportunity to model epithelial barrier dynamics, cellular differentiation, and proliferation more accurately in specific intestinal segments and in tissue containing a proportional representation of the diverse epithelial subtypes found in the native gut greatly enhances the translational potential of organotypic gastrointestinal culture systems. By using these tools, researchers have uncovered novel aspects of host–pathogen and host–symbiont interactions with the intestinal epithelium. Application of these tools promises to reveal new insights into the pathogenesis of infectious disease, inflammation, cancer, and the role of microorganisms in intestinal development. This review summarizes research on the use of gastrointestinal organoids as a model of the host–microbe interface. *(Cell Mol Gastroenterol Hepatol 2017;3:138–149; http://dx.doi.org/10.1016/j.jcmgh.2016.11.007)*

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2009 was a landmark year in the field of gastroenterology, because it was the first time that primary non-transformed tissues derived from the gastrointestinal (GI) tract was shown to have the capability of long-term growth in vitro.[1,2] These studies successfully led to the maintenance and propagation of 3-dimensional (3D) tissue that maintained some properties of the complex intestine in vivo. For example, isolated intestine could be grown as epithelium-only structures[1] or as epithelium plus supporting stromal/mesenchymal tissue.[2] A defining feature of these seminal works was the creation of an artificial niche in vitro, which promoted the maintenance of the highly proliferative intestinal stem cell population. This artificial niche is complex and requires the proper physical environment (extracellular matrix [ECM]) and chemical environment (growth factor signaling) to mimic, in part, the environment found in the native gut.[1,2] Collectively, these organotypic cultures represent a complex system for studying the intestine and commonly are called *organoids* because they retain organ-like features, such as the plethora of differentiated epithelial cell types (goblet, Paneth, enteroendocrine, enterocyte).[3]

Since these early days, well shy of a decade ago, diverse tissues of the gastrointestinal tract have been grown from primary human and mouse tissue sources, including esophagus, liver, pancreas, stomach, and colon.[4–13] In addition to long-term culture of organ-derived tissues, the development of an artificial niche also prompted advances in research involving the differentiation of human embryonic and induced pluripotent stem cells (collectively called hPSCs) into 3D organoids. To date, hPSCs have been differentiated into GI tissues including small intestine, stomach (antrum), and liver.[14–19] A rapidly expanding body of literature has emerged surrounding the applications of organoids, and intestinal organoids in particular, as model systems to study human development and disease in vitro (Figure 1).[20,21]

Human organoids, whether derived from donor tissue or from hPSCs, represent important tools to probe human gastrointestinal biology, physiology, and pathophysiology.

Abbreviations used in this paper: **CDI, *Clostridium difficile* infection; ECM, extracellular matrix; GI, gastrointestinal; HIO, human intestinal organoids; hPSC, human pluripotent stem cell; IFN, interferon; IL, interleukin; NEC, necrotizing enterocolitis; SCFA, short-chain fatty acid; TcdB, *C difficile* toxin B; 3D, 3-dimensional.**

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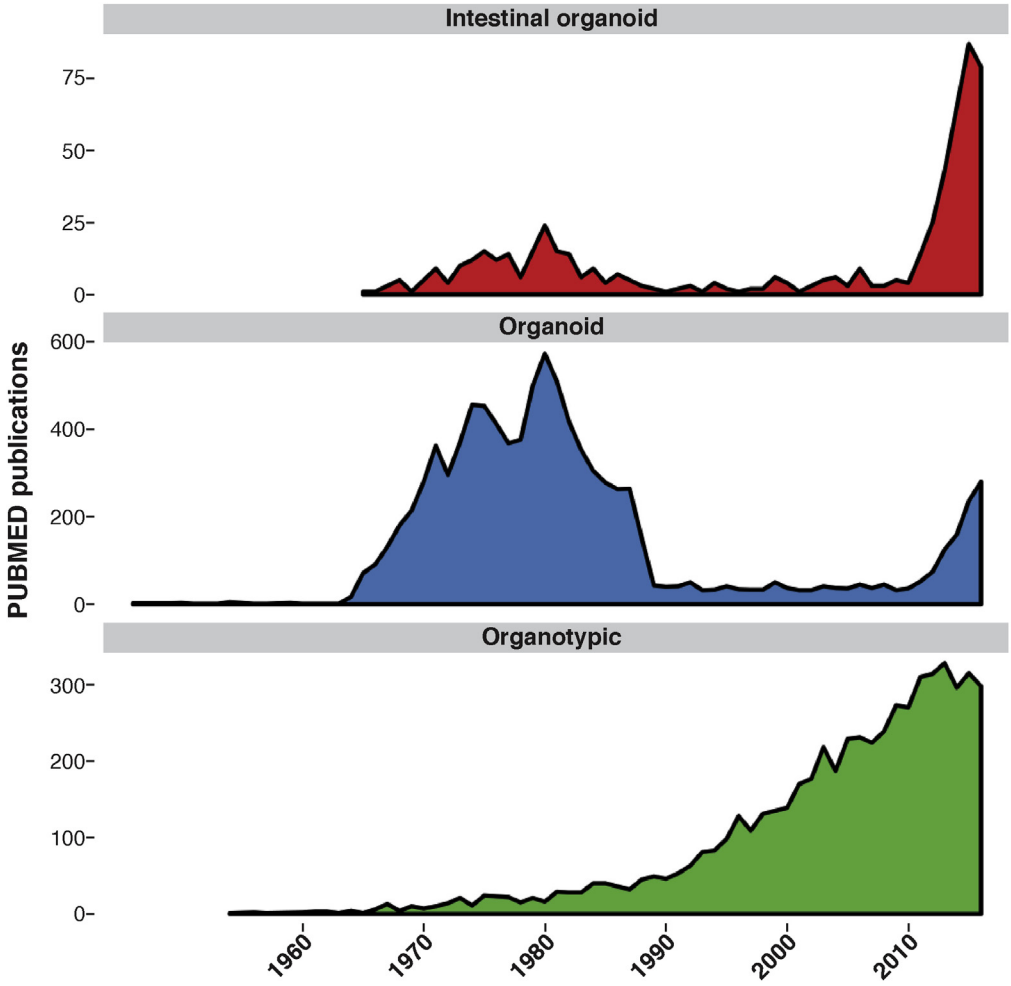

Figure 1. The number of citations referencing intestinal organoids has increased dramatically over the past decade. Notably, the term *organoid* was at one time commonly used in reference to organoid nevus, an uncommon type of benign hair follicle tumor that is now known as a sebaceous nevus.[29]

Among the essential roles of the intestinal epithelial barrier is the maintenance of a continuous surface that must perform necessary absorptive functions, and that must interface with microbes to create an environment that simultaneously permits colonization by beneficial organisms and excludes opportunistic pathogens.[22] Perturbations in this dynamic symbiosis underlie the pathogenesis of inflammatory disease,[23,24] gastrointestinal cancer,[25] metabolic syndrome,[26] and other conditions.[27,28] However, the mechanistic basis of host–pathogen and host–symbiont interactions in the human intestine is not well understood. This review focuses on the application of gastrointestinal organoids as a model of the host–microbe interface.

Defining Gastrointestinal Organoids

The rapid growth in the number of investigators using diverse 3D intestinal tissue culture systems (Figure 1) has outpaced the adoption of standardized nomenclature. Cultured tissues that retain some amount of complex in vivo function and cellular diversity are considered "organotypic,"[3] a term encompassing both cultured whole-tissue explants[30] and organoids.[1,14,31] However, given the plethora of models now available as research tools, it is important to keep in mind that not all organoids are directly comparable.[3] For example, tissue-derived organoids can be grown with[2,32] or without[1,33] mesenchyme, and are ideal for modeling adult homeostasis or disease.[32,34–36] On the other hand, hPSC-derived organoids are more similar to immature (fetal) tissue than to adult tissues,[16,37–39] but become more adult-like after transplantation into a living mouse host.[38,40,41] For the purposes of the current review, we refer to organoids derived from human tissue/organs as tissue-derived organoids and we specify if tissue-derived organoids are epithelium-only or grown with the epithelium and mesenchyme, and we refer to organoids derived from hPSCs as *hPSC-derived organoids* (Table 1).

Improved Models of the Gastrointestinal Tract

Cell lines have been an important work horse of in vitro gastrointestinal experimentation for decades, and have led to major insights, but also have some limitations.[42–44] Explant tissue models, in which intestinal tissues are removed from model organisms, dissected from patient samples or collected from human organ donors offer the full spectrum of cellular diversity and intestinal