Intestinal Organoids: New Frontiers in the Study of Intestinal Disease and Physiology

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ABSTRACT

The development of sustainable intestinal organoid cell culture has emerged as a new modality for the study of intestinal function and cellular processes. Organoid culture is providing a new testbed for therapeutic research and development. Intestinal organoids, self-renewing 3-dimensional structures comprised intestinal stem cells and their differentiated epithelial progeny allow for more facile and robust exploration of cellular activity, cell organization and structure, genetic manipulation, and vastly more physiologic modeling of intestinal response to stimuli as compared to traditional 2-dimensional cell line cultures. Intestinal organoids are affecting a wide variety of research into gastrointestinal pathology. The purpose of this review is to discuss the current state-of-the-art and future effect of research using enteroids and colonoids (organoids grown from the small and large intestines, respectively).

Key Words: colonoid, enteroid, intestinal organoid, intestinal stem cell, *lgr5*, precision medicine

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What Is Known

- Intestinal stem cells are self-renewing pluripotent stem cells inhabiting the intestinal crypt.
- Intestinal stem cells can be experimentally induced to create a functional recapitulation of the large and small intestinal epithelium.

What Is New

- Intestinal organoids are currently being used to study a variety of host-pathogen interactions.
- Intestinal organoids serve as a useful platform for drug screening and personalized medicine.
- Disease-specific ex vivo models can be created from patient-derived material.
- Intestinal organoids may someday support the creation of tissue-engineered small intestines.

Accurate models of biological systems are vital to the advancement of all biosciences. The pursuit of a reliable and accurate ex vivo model of intestinal function has attracted much interest, owing to the limitations of existing 2-dimensional (2D) immortalized cell line–based systems. Heretofore, intestinal epithelial cells (IECs) would rapidly undergo anoikis (a form of apoptosis) following isolation, preventing establishment of primary, nontransformed IEC cultures. Building upon the earlier success of short-term intestinal crypt cell culture on collagen-coated vessels, the Clevers laboratory succeeded in the creation of the first self-renewing, nontransformed minigut organoid culture (1). This significant advancement created a new way to study the function of the intestinal epithelium, yielding an accessible platform for basic and translational experimentation in a physiologically relevant context.

The pursuit of an ex vivo model of intestinal function has been a long one, beginning with initial success in growing adult crypt cells on collagen-coated vessels, which could be propagated for short periods of time (2). This evolved through efforts by Ootani et al (3) to establish a culture system based on an air-liquid interface in which neonatal intestinal mucosa (epithelium and mesenchyme) formed long-lasting organoid structures. The common ground between these systems is the requirement for mesenchymal fibroblasts, without which propagation is impossible. In 2009, Sato et al established a platform for organoid growth and propagation that broke free of mesenchymal dependence, instead employing a defined set of intestinal stem cell (ISC) niche factors. This work simplified the process of growing and maintaining intestinal crypt cultures and expanded the variety of potential source material.

An organoid is defined as a miniature organ grown in vitro. It can be produced via adult multipotent stem cells or induced pluripotent cells (iPS) cultured in a stromal replacement such as Matrigel. Importantly, adult intestinal multipotent stem cells are limited in differentiation to intestinal epithelium, whereas iPS cells, derived from embryonic stem cells or reprogramed from adult tissue, can be driven to differentiate into a broader array of cells (4). When referring to intestinal organoids, the source of the harvested tissue further defines the structure and characteristics of the resulting organoid. Tissue harvested from the small intestine will recapitulate small intestinal function and structure, and is termed an ''enteroid,'' based on National Institutes of Health–sponsored consensus guidelines (5). Similarly, cells harvested from the colon will recapitulate the colon, creating a ''colonoid.'' Intestinal organoids can be produced from either isolated ISCs or stem cell–containing intestinal crypts. Both methods result in growth of a 3-dimensional (3D) structure of epithelial cells. The structure of these cells will resemble their in vivo organization when

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