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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Rebuttal to: In Vivo Studies Should Take Priority When Defining Mechanisms of Intestinal Crypt Morphogenesis

See Point-Counterpoint articles on pages X and X.

Guiu et al argued that organoids do not always reflect in vivo crypt morphogenesis. Organoids consist of all types of epithelial cells, but do not include stroma that is required to instruct proper crypt morphogenesis. Therefore, it would be realistic to use in vivo mouse models for studying postnatal crypt morphogenesis. However, we would like to emphasize that organoids have crypt-forming potential, because we have seen crypt formation in orthotopically transplanted mucosa in vivo.[1,2] Further refinement of organoid culture system, such as coculturing with mesenchymal cells, might enable us to study crypt morphogenesis more accurately. There is a great advantage in using organoids for studies where extrapolation of organoids to in vivo studies has been confirmed or can only be confirmed in human cells.

In addition, Guiu et al emphasized the importance of extracellular matrix (ECM). The morphology of organoids is indeed influenced by the stiffness of the ECM and the endogenous cellular forces, and can sometimes be difficult to interpret. Although our understanding of organoid mechanobiology was limited because of the limitations of the analytical methods, a recent study confirmed a substantial agreement between organoids and the intestinal epithelium in vivo.[3] Intestinal organoids can capture the cellular morphology and cytoskeletal organization of the in vivo crypt structure. Obviously, in vivo comparison is necessary for the first validation that organoids reflect the in vivo state. There are a variety of ECM/scaffolds used in organoid research, such as Matrigel (Corning Life Sciences, Tewksbury, MA),[2] collagen gel,[1] hydrogel,[3] the decellularized human intestinal scaffolds,[4] and the perfusable tube scaffolds emulating crypt structures.[5] These ECM/scaffolds may support organoid formation resembling in vivo crypt structures.

As Guiu et al pointed out, in vivo mouse study could reveal crypt morphogenesis in a holistic fashion, whereas organoid uses a reductionistic approach. We think reductionistic approach has strong advantages to understand a functional contribution of individual factor in crypt morphogenesis and to perform high-throughput screening. Thus, combined approaches (in vivo mouse experiments and in vitro organoids) will ultimately reveal novel insights into crypt morphogenesis and may open up a new area for biophysical regulation of intestinal epithelial morphology.

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Conflicts of interest
Toshiro Sato is an inventor on several patents related to organoid culture. The remaining author discloses no conflicts.

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