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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Rebuttal to: Organoid vs Mouse Model: Which is a Better Research Tool to Understand the Biologic Mechanisms of Intestinal Epithelium?

See Point-Counterpoint articles on pages X and X.

There are obvious pros and cons when choosing an in vitro and in vivo model for addressing biologic questions. This has been clearly outlined in both ours and the commentary by Drs Sugimoto and Sato. Evidently, one should always strive to take advantage of a combination of different models to address research questions in a comprehensive manner and ascertain that observations are physiologically relevant.

It goes without saying that the organoid technology has been transformative for the field of intestinal biology, because it has increased the ability to address mechanistic questions in cells derived from experimental animal models and healthy and diseased human tissues. This has opened up vast opportunities to address new and more challenging questions; however, we would like to stress that nowadays in vitro findings should be supported by in vivo studies. Our counterpoints to the commentary by Drs Sugimoto and Sato are the following.

First, we agree that the organoid model provides unprecedented opportunities for studying the human intestinal epithelium. Yet, there are still complex processes that involve several tissues and/or organs, which cannot be modeled (eg, gut-brain axis or endocrine role of the intestine). Moreover, whereas organoids may simulate, for example, intestinal lineage differentiation, it is more complicated to model in vivo epithelial behavior. Here it is important to also note that cells in organoids irrespective of the location are exposed to similar microenvironments, which are unlike those associated with complex organs in vivo.[1] A future avenue could consequently be to develop structured organoid models containing multiple different cell types and/or tissues. Here one could envision that cocultures of epithelium with mesenchyme or immune cells will provide further insight into how cell fate is regulated.[2]

Second, we completely agree that a major advantage of the organoid technology is the throughput for identifying drugs or genes that affect a particular cell behavior or differentiation along a particular lineage.[3] Yet, one can still argue that the limitations are the same as for the previous point, and that it is important to keep in mind that organoids represent a reductionistic in vitro model lacking the spatial and cellular complexity observed in vivo.

Third, we would like to stress that researchers need to be extremely careful, when it comes to nomenclature. Organoids do not resemble an organ, because they typically only include a single tissue. An organoid is not a minigut, a bud on an organoid is not a crypt, nor are the domains that connect buds villi. It is consequently impossible to extrapolate findings directly from organoids to physiological processes (eg, crypt morphogenesis and crypt fissioning). It will be important in the future to align the studies of organoids with those of the in vivo tissue to address which biologic processes can be rightfully modelled in vitro using organoids. As we discuss in our commentary, we strongly believe that the complex and dynamic in vivo interplay between epithelium and mesenchyme will be complicated if not impossible to fully simulate in vitro.

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