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Mini Review

Integration of Farm Animal Intestinal Organoids and Gut-on-a-Chip: One Health Initiatives

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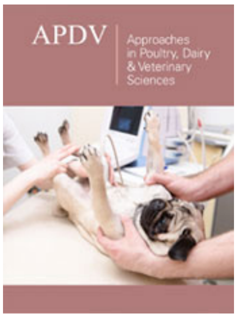

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Abstract

Intestinal organoid models derived from farm animals have great potential to contribute to both agriculture and human health as a one health initiative, which recognize a cohesive relationship among farm animals, humans, and their shared environment. This is because the Three-Dimensional (3D) organoids maintain the self-organizing and self-renewing properties as well as the high structural and functional similarities to the originating donor tissues [1]. Intestinal organoids from farm animals could play an important role in investigations of the pathophysiology of enteropathogens that could lead to chronic wasting disease and low agricultural production or zoonotic diseases that poses significant threats to public health [2]. Here, we discuss the integration of intestinal organoid culture and gut-on-a-chip systems in farm animals to potentially overcome current limitations in in vitro studies in public health and food security as one health initiatives. We envision multidisciplinary work integrating intestinal organoid culture and microfluidic gut-on-a-chip technology can contribute to improving both human and farm animal health.

Keywords: Farm animals; Intestinal organoid; Gut-on-a-chip; One health; Public health

Abbreviations: 3D: Three-Dimensional; PEDV: Porcine Epidemic Diarrhea Virus; PDCoV: Porcine Deltacoronavirus; TGEV : Transmissible Gastroenteritis Virus

Mini Review

In the last ten years, technological advancement was made in 3D intestinal organoid culture [1,2] and successful development of intestinal organoids has been reported in various farm animal species including pigs [3-6], cattle [7-10], sheep [11], horse [11,12], and chicken [11,13,14]. Intestinal organoids of these species have been used in *in vitro* investigation of epithelium-microbe interactions and modelling of enteropathogenesis of various bacterial, viral and parasitic infections [3,9,15,16]. These studies suggested the importance of 3D intestinal organoid culture in public health and agricultural management due to its relevance and translatability to the public health by shedding lights into disease pathogenesis or therapeutic targets. Despite their promising features as powerful tools for basic and applied research [1], intestinal organoids hold clear limitations to develop more complex systems which better represent dynamic tissue-pathogen interactions occurring *in vivo* organs. Specifically, the enclosed luminal surface within the 3D intestinal organoids makes the investigation of host-pathogen or host-xenobiotic interaction limited [17]. Moreover, the static nature of the culture system does not mirror the dynamic nature of the intestinal tract and is not suitable for a long-term co-culture with host intestinal cells and microbial cells (i.e., microbiome or enteric pathogens) to investigate their crosstalk [18].

To overcome these challenges, integration of organoid and organ-on-a-chip system has been suggested recently [18-20] and applied in farm animal research [21,22]. Most of the microfluidic, gut-on-a-chip technology offer a continuous removal of the waste product of host and bacterial cells and supply continuous nutrients [23]. The shear stress applied by the fluid flow works as a dynamic force to stimulate the host intestinal cells and stimulate physiologic growth [24]. Some of the gut-on-a-chip devices allow application of peristaltic like motion to better mimic dynamic environment in the gut which minimizes the bacterial overgrowth in the systems [18]. Various other cell types (i.e., endothelial cells [25] or immune cells [26]) have been integrated into gut-on-a-chip devices to further adding the complexity to the model systems. Moreover, some of the devices allow modification of oxygen levels allowing the culture of anaerobic bacterial cells while maintaining the growth of host intestinal epithelial cells to better mimic the oxygen gradient present in the gut [27,28]. Further advances in the gut-on-a-chip technology and its application with intestinal organoids would greatly improve our understanding of fundamental biology and pathology, thus enhancing health care management of both farm animals and people (Figure 1). Studies on infectious diseases using such multidisciplinary technology would not only contribute to improving production efficiency of farm animals through decreased morbidity and mortality but also minimize economical damage for enteric infectious disease management. Viral enteric pathogens (e.g., Porcine Epidemic Diarrhea Virus (PEDV) [29], Porcine Deltacoronavirus (PDCoV) [5], and Transmissible Gastroenteritis Virus (TGEV) [30]) have significant economic impact in the pig industry due to high morbidity and mortality in piglets [31] while no effective *in vitro* models exist to study these diseases. Knowledge obtained through the multidisciplinary work of intestinal organoids and gut-on-a-chip would offer new insights to improve herd health management, contributing to the reduction of economic losses as well as the increase in agricultural production.

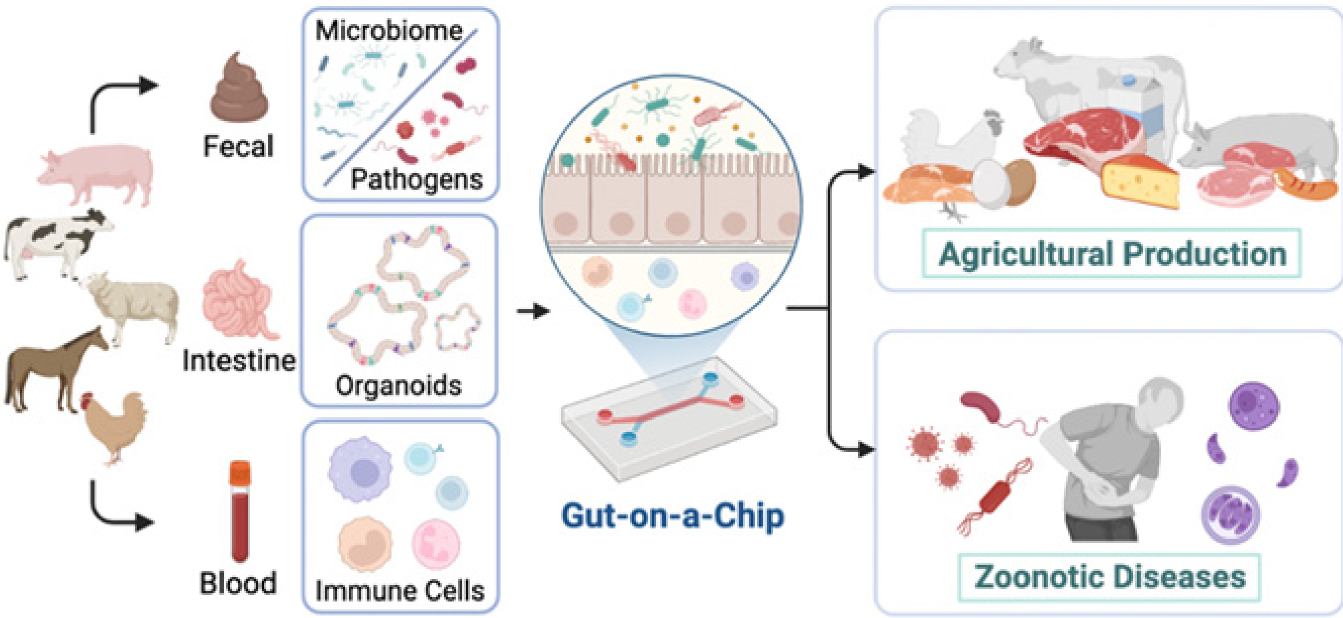

Figure 1: One Health initiatives with the integration of farm animal intestinal organoids and gut-on-a-chip technology. Integration of intestinal organoids from various farm animal species and organ-on-a-chip technologies enables the creation of a gut environment that is more similar to *in vivo* by culturing intestinal organoids in the upper microchannels, adding microorganisms (microbiome and/or enteric pathogens) to the epithelial surface layer, while allowing blood-derived immune cells to flow into the lower microchannels. Mechanistic and novel therapeutic investigations of various enteropathogenic and wasting diseases can be performed, which could ultimately lead to improve the agricultural production. Investigations of host-pathogen interactions in zoonotic infectious diseases can improve public health through better understanding of the pathophysiology and potential discovery of new therapeutic strategy for the diseases. Created with BioRender.com.

Another potentially important application of the integration of intestinal organoids and gut-on-a-chip models to study various types of enteropathogenic pathogens where the current *in vitro* models have limited ability to recapitulate (e.g., *Salmonella typhimurium* [16], *Escherichia coli* [8], *Toxoplasma gondii* [16], and *Giardia duodenalis* [32]). Farm animals play a pivotal role in public health because they can be reservoirs of various zoonotic diseases [33]. Some pathogens can be clinical or subclinical diseases to farm animals leading to long-term contamination of the environment and infect humans which can lead to severe diseases in susceptible individuals leading to epidemics. Since many of these pathogens can have host specificity, gut-on-a-chip models derived from farm animal intestinal organoids could serve as a good model to study host-pathogen interactions and potential protective mechanisms of hosts when intestinal organoids of asymptomatic carrier species are used [34]. The multidisciplinary work of intestinal organoids and gut-on-a-chip would offer a useful alternative to animal models, which not only hold ethical challenges but also require many resources in labor and housing facilities [2]. Furthermore, enteric infection models using gut-on-a-chip technology could serve as useful tools for screening efficacy and adverse events of vaccines and antibiotics against various enteric infectious diseases, thus ultimately contributing to improve public health.

Conclusion

The establishing intestinal models of farm animals integrating 3D intestinal organoid culture and gut-on-a-chip systems could lead to deeper insights in physiological and pathological conditions through one health initiatives. Such tools can be used to provide new insights for improving heard health and agricultural productivity through improved disease management, leading to sustainable food production, or to investigate host-pathogen interactions and host defense mechanisms against zoonotic infectious diseases. Moreover, this multidisciplinary work can provide critical complexities to the experimental designs to support the 3R principles (reduce, refine, and replace) [35] and contribute to the health and welfare of livestock.

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