Human organoid-derived Gut-on-Chip model for studying Virus-Host interactions

Commonly used acronym: *Gut-on-chip model*

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Specific Research Group or Service

PORTO Lab - Pathogenesis Of RNA viruses & Therapeutic Options
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SCOPE OF THE METHOD

The Method relates to	Human health

The Method is situated in	Basic Research, Translational - Applied Research
Type of method	In vitro - Ex vivo
Specify the type of cells/tissues/organs	Human intestinal enteroids derived from human small intestine tissue

DESCRIPTION

Method keywords

enteroids

gut-on-chip

microfluidic systems

organoid-on-chip

co-culture

Scientific area keywords

Human intestinal organoids

gastroenteric viruses

viral infection

infectious disease

Method description

Organ-on-Chip (OoC) systems are an emerging cell culture technology that bridge the gap between conventional 2D culture and animal models or patients. These microfluidic systems typically consist of one or more compartments containing tissue-specific cells grown on scaffolds such as membranes or hydrogels. OoC models can recapitulate key organotypic functions, while integrated pumps provide continuous microfluidic perfusion to mimic blood flow, resulting in the removal of waste, providing nutrients and growth factors, thus overall better mimic essential *in vivo* conditions. We established an

adult stem cell–derived human intestinal organoid gut-on-chip system using Dynamic42 biochips to study virus–host interactions. The model integrates human intestinal epithelial cells that self-organize into a 3D architecture featuring villus- and crypt-like structures. The biochip is cultured connected to a peristaltic pump that perfuses the culture medium. Each biochip contains two microfluidic chambers separated by a porous polyethylene terephthalate (PET) membrane, which serves both as a scaffold for cell attachment and as a semi-permeable barrier enabling cell–cell communication and migration. Each chamber is accessible via two Luer-lock ports. Upon perfusion, the cells form 3D structures that provide a physiologically relevant interface for colonization with live microorganisms. Virus infection can be performed under static or perfused conditions. Multiple readouts can be applied to both effluent and tissue layers, including assessment of viral replication kinetics (RT-qPCR), virus tropism (confocal microscopy), cell viability, metabolic activity, immune responses, barrier integrity, and single-cell RNA sequencing.

Lab equipment

Biochips, peristaltic pump,

silicon tubes,

Luer caps and connectors,

biosafety cabinet,

CO2 cell incubator,

refrigerated centrifuge,

microscope,

micropipettes.

Method status

Still in development

Internally validated

PROS, CONS & FUTURE POTENTIAL

Advantages

- Gut-on-chip (GoC) devices enable continuous perfusion of culture medium, generating shear stress and nutrient flow that more closely replicate the *in vivo* intestinal microenvironment compared to static culture systems.
- OoC platforms allow precise control of biochemical gradients, oxygen levels, and flow dynamics—key factors for establishing *in vivo*-like tissue barriers and studying host–pathogen interactions.
- Furthermore, these models reproduce not only the structural and molecular characteristics of human organs but also their biomechanical cues, making them highly relevant for research and development that require physiologically representative human systems.
- When integrated with immune cells, OoC systems can also mimic aspects of the human intestinal immune response.
- Use of commercially available biochips help implementation of the system in the lab.

Challenges

- Cost and accessibility: Devices, pumps, and specialized expertise remain expensive and not widely available.
- Lack of standardized designs, materials, and operating parameters makes comparison between studies difficult.
- The system has low throughput.
- Maintaining differentiated phenotypes and viable co-cultures under flow for extended periods is difficult.
- Replication of the immune system *in vitro* remains complex and often oversimplified.

Modifications

- A multilayered gut-on-chip, including intestinal epithelial cells, endothelial cells and immune cells, is being explored.

Future & Other applications

- The gut-on-chip model can also be used to study drug interactions, co-infection and can be connected to other organ-on-chip systems.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

References

Maurer M, Gresnigt MS, Last A, Wollny T, Berlinghof F, Pospich R, Cseresnyes Z, Medyukhina A, Graf K, Gröger M, Raasch M, Siwczak F, Nietzsche S, Jacobsen ID, Figge MT, Hube B, Huber O, Mosig AS. A three-dimensional immunocompetent intestine-on-chip model as in vitro platform for functional and microbial interaction studies. Biomaterials. 2019 Nov;220:119396. doi: 10.1016/j.biomaterials.2019.119396. Epub 2019 Aug 2. PMID: 31398556.

Feile A, Wegner VD, Raasch M, Mosig AS. Immunocompetent Intestine-on-Chip Model for Analyzing Gut Mucosal Immune Responses. J Vis Exp. 2024 May 24;(207). doi: 10.3791/66603. PMID: 38856194.

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