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Review Article

New methodologies for old problems: tridimensional gastrointestinal organoids and guts-on-a-chip

*Marna Eliana Sakalem**, *João Tadeu Ribeiro-Paes*

Universidade Estadual Paulista (UNESP), Laboratório de Genética e Terapia Celular (GenTe Cel), São Paulo, SP, Brazil

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ABSTRACT

Objectives: The present review intended to present a critical overview of the methodological and experimental advances concerning tridimensional cell culture models within the scope of gastrointestinal research.
Methods: A literature review was performed and some of the main published articles in the area were mentioned.
Main results: Classic studies and high impact results were presented, starting from the pioneer works with gastrointestinal organoids, with a small gut organoid, to the achievement of guts-on-a-chip and multi-organ-chips. It was also discussed which implications the construction of such co-cultures bring, as well as future applications arising from these new methodologies.
Conclusions: Despite the still discrete number of publications, in quantitative terms, there are qualitative promising and consistent results addressing physiopathological aspects and new therapeutic perspectives of tridimensional in vitro cultures in the gastroenterology field. It is expected, thus, that such new methodological approaches, including organoids and guts-on-a-chip, may contribute decisively to the advance in knowledge on basic aspects, as well as on the translation to new therapeutic approaches in gastrointestinal diseases.

Novas metodologias para velhos problemas: organoides gastrointestinais e guts-on-a-chip tridimensionais

Palavras-chave:
Organoides
Organs-on-a-chip
Gut-on-a-chip

RESUMO

Objetivos: A presente revisão visou apresentar uma abordagem crítica dos avanços metodológicos e experimentais referentes a modelos de cultura celular tridimensionais no âmbito do sistema gastrintestinal.

* *Corresponding author.*
E-mail: marna7@gmail.com (M.E. Sakalem).

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Modelos in vitro tridimensionais
Gastrintestinal

Métodos: Foi realizada revisão da literatura com ênfase nos principais artigos publicados na área.

Resultados principais: São apresentados trabalhos clássicos e resultados de maior impacto, desde os trabalhos pioneiros com organoides do sistema gastrintestinal, com intestino delgado, até a obtenção de *guts-on-a-chip* e *multi-organ-chips*. Discutiu-se, ainda, as implicações decorrentes da elaboração de tais co-culturas, bem como as futuras aplicações decorrentes dessas novas metodologias.

Conclusões: Apesar do número ainda discreto de publicações, em termos quantitativos, há, qualitativamente, resultados promissores e consistentes abordando aspectos fisiopatológicos e de novas perspectivas terapêuticas em gastrenterologia decorrentes das culturas tridimensionais in vitro. É esperado, portanto, que essas novas abordagens metodológicas incluindo organoides e *guts-on-a-chip* possam contribuir decisivamente para o avanço no conhecimento sobre de aspectos básicos, bem como para a translação do conhecimento para novas abordagens terapêuticas em doenças gastrintestinais.

Preclinical studies, which involve both animal and in vitro research, have enabled a vast part of what is known in life sciences today, and have significantly contributed to the comprehension of human anatomophysiology and pathology, as well as for the development of new drugs and therapeutic approaches in different branches of medical specialties. Such investigations are crucial to achieve a better understanding of the development and triggering of diverse diseases, as well as to test efficacy and safety of new therapeutic approaches, which can be further brought to clinical experimentation and, then, as consequence, could be applied in human patients.

Animal models are the most common tools in health-related investigations and have been attributed to more than 70% of biomedical advances.[1] Amongst the advantages of animal experimentation, which rely mostly on rodent models, are the ease to breed animals under laboratorial conditions, obtain large numbers of individuals in a relatively short time, and the possibility of developing transgenic lineages for specific purposes.[2] In the spectrum of gastrointestinal diseases, the use of animal research is valuable due to the similarity between rodent and human gastrointestinal systems, and thus allows the investigation of different stages of intestinal diseases, from the development of the first symptoms to the complete establishment of the pathology.[3] On the other hand, there are important divergences between model and human reality, such as differences in the intestinal microbiota composition,[4] alongside with the ethic concern on the use of animals for research purposes, what evidences the urge for suitable experimental alternatives.

The search for methodologies that represent a better translation between basic research and therapeutic application, at the same time that substitute methods for animal models are highly desired, has led to the development of new experimental in vitro approaches. The classical bidimensional cell cultures have been an important tool for the analysis of molecular and biochemical aspects in life sciences, also as a complement to the researches using animal experimentation. The uniformity of the cell types composing the bidimensional (2D) cell cultures allow an advantageous standardization for morphological and functional studies; nevertheless, this very same standardization represents a limitation of such methods in relation to the representation of physiological and pathological aspects as a whole, meaning they fail to support the different cell types and structure of an organ.[5] Therefore, tridimensional (3D) cell cultures have gained increased attention in the last decade.[6]

The 3D models are mostly composed by different cell types of the desired organ or tissue that self-organize into a tissue architecture, and thus allow a more specific and more realistic representation of a live tissue, what could not be achieved using monotype 2D cultures. The most recent investigations and protocols using three-dimensional cultures already show models which simulate several organs/systems interconnected, representing, at least partially, a human being in an in vitro assay ('human-on-a-chip' or 'lab-on-a-chip', see Marx et al.[7] and Abaci et al.[8] for review).

The most known tridimensional culture method is the organoid, named due to its capacity to mimic, at least partially, structure and function of a live organ, although its size rarely surpasses some millimeters; 'oid' comes from the Latin 'oides', and means resemblance.[9] Either starting from adult or pluripotent stem cells, the formation of the organoid can be achieved using two main principles: the multi-type cell culture is either set up by the experimenter, or the stem cells are orchestrated into the desired tissue by inducing factors and build the three-dimensional structure spontaneously, as they differentiate. For the first approach, the different cell types are differentiated from stem cells or obtained separately, cultivated in different flasks and then set together in the same environment along with an extracellular matrix, and aggregate in form of pellets or spheroids[10–12]; this aggregation can be performed, for example, using magnetic levitation to handle each cell culture separately, and further unite them in a desired order in the same flask.[12,13] For the spontaneous formation, the stem cells are grown on proteins gels or synthetic polymers, or even in regular dishes with culture medium, and spontaneously form the different layers and structure of the desired tissue or organ as they differentiate, responding to the environmental, in vitro, cues.[14] Either way, the cell aggregation leads to a 3D structure that allows the reproduction of

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