Organ-on-Chip

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Organ-on-chip (OOC) devices are *in vitro* miniaturized multicellular systems with defined architectures that represent the new frontier in biomedical research to produce micro-organoids and tissues for drug testing and regenerative medicine.

Although OOC devices can potentially improve the prediction capability of preclinical studies in comparison to *in vitro* tests and animal models, the successful transition from conventional 2D cell culture to human OOC implies the development of microfluidically supported 3D architectures to mimic the native extracellular matrix (ECM), to induce cell-ECM and multicellular interactions, as well as to modulate many cell functions including polarity, morphology, and motility.

In this regard, cell-laden microgels (CLMs) represent a promising tool for 3D cell culturing and on-chip generation of micro-organs.

Keywords: organ-on chip ; 3D culture ; cell-laden microgels ; microencapsulation ; compartmentalization ; single-cell encapsulation

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This focused entry provides an overview of the most recent applications of cell-laden microgels (CLMs) in microfluidic devices for organoids formation, highlighting microgels' roles in organ-on-chip (OOC) development as well as insights into future research.

These microgels can resemble the functional organ sub-units and serve as building blocks to be assembled into 3D tunable tissue constructs. Overall, the microgels' intrinsic features, such as high surface-to-volume ratio, spatial confinement, high tunability of both chemical/physical cues, and spatial assembly, make them ideal platforms to develop on-chip 3D tissue models that resemble cell–cell and cell–ECM interactions in a biomimetic microenvironment.

Here, we first discussed the encapsulation of cells into microgels (*i.e.* microencapsulation), highlighting how it represents the premise for most of the microgels' functions within the OOC and microfluidic devices. Then, the main applications of CLMs in the development of OOC and microfluidic platforms, namely compartmentalization, single-cell encapsulation, and control on proliferation, polarity and cell fate were argued. Since the focus of this work is on organoids and micro-organs formation on-chip, we will not review non-structured 3D aggregates or spheroids. Furthermore, the capability of microgels to encapsulate and release bioactive molecules in a controlled manner has not been considered.

1. Microencapsulation and Cellular Confinement

The integration of microgels in on-chip cell culture can be achieved through two main strategies: cells can be deposited and cultured on the microgel surface or encapsulated into the microgel matrix [1]. Despite the first approach (cell deposition on microgel surface) is characterized by high controllability and ease of cell manipulation, it has also typical limitations of 2D cell culture, being unable to accurately mimic the *in vivo* microenvironment provided by the ECM. Differently, microencapsulation is an attractive technique for 3D cell culture, since the microgel polymeric chains enable a more accurate mimicry of the complex 3D networks of macromolecules composing the ECM.

2. Applications of Microgels in OOC

The application of CLMs in OOC represents an attractive tool to realistically mimic tissue models and organs, that are typically built from repeated, microscale functional units. [2] Indeed, spatially controlled assembly of CLMs results in architectures that reproduce modular tissue constructs while monitoring the microenvironment of individual cell types, [3][4] and enable the signaling experienced by cells *in vivo.* [5]

2.1. Compartmentalization

Living tissues have an intrinsic heterogeneity due to the presence of highly organized, different cell types in ECM components. Mimicking this structural complexity is a key point to faithfully fabricate tissue/disease models and micro-organs and achieve affordable results in fundamental biological studies, drug screening and toxicity assessment as well as tissue transplantation and cell therapy [2]. To this aim, there is the need to spatially pattern multiple cell types in biocompatible ECM matrices, *i.e.* to compartmentalize the microfluidic 3D culture [1] that can be achieved through different strategies, including lithography and 3D printing. [6] Microgels represent an attractive bottom-up strategy for compartmentalization, since they can be assembled in complex, multiphasic, and highly modular architectures without using complex chemistry.

2.2. Single Cell Culture

Single-cell analysis has emerged as a powerful tool in biological and biomedical research for providing insights into the complex interplay between cell populations *in vitro* and *in vivo* [7]. Compared to larger hydrogels, microgels are more attractive model systems for studying cells at a single level, since they allow for efficient encapsulation of individual cells into a gel matrix with dimensions comparable to the cell size. Furthermore, microgels provide individual cells with a highly versatile, controllable, and reproducible microenvironment that allows them to be independently cultured, manipulated, and analyzed. [7]

2.3. Control on Proliferation, Polarity and Cell Fate

Although stem cells can differentiate into any type of cell in the adult body, it is often difficult to control microenvironmental factors that induce differentiation pathways. Microgels represent an attractive, scalable strategy for tailoring the stem cell microenvironment, since they can provide well-defined, uniform, and compartmentalized cell cultures. As an additional tool to control the cellular microenvironment, microgels can encapsulate and release in a controlled manner growth factors. [8]

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