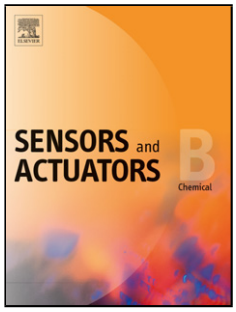

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Spheroids-on-a-chip: Recent advances and design considerations in microfluidic platforms for spheroid formation and culture

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Highlights

- Cell spheroids are spherical aggregates best mimicking the tissue microenvironment.
- Spheroid culture better recapitulates the in-vivo condition in microfluidic chips.
- Microfluidics provides rapid spheroid formation with size uniformity and control.
- These chips contain microwells, microstructures, droplet generators, etc.
- To fabricate such chips, some design considerations must be taken into account.

Abstract

A cell spheroid is a *three-dimensional (3D)* aggregation of cells. Synthetic, *in-vitro* spheroids provide similar metabolism, proliferation, and species concentration gradients to those found *in-vivo*. For instance, cancer cell spheroids have been demonstrated to mimic *in-vivo* tumor microenvironments, and are thus suitable for *in-vitro* drug screening. The first part of this paper discusses the latest microfluidic designs for spheroid formation and culture, comparing their strategies and efficacy. The most recent microfluidic techniques for spheroid formation utilize emulsion, microwells, U-shaped microstructures, or digital microfluidics. The engineering aspects underpinning spheroid formation in these microfluidic devices are therefore considered. In the second part of this paper, design considerations for microfluidic spheroid formation chips and microfluidic spheroid culture chips (μSFCs and μSCCs) are evaluated with regard to key parameters affecting spheroid formation, including shear stress, spheroid diameter, culture medium delivery and flow rate. This review is intended to benefit the microfluidics community by contributing to improved design and engineering of microfluidic chips capable of forming and/or culturing three-dimensional cell spheroids.