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Advantages and challenges of microfluidic cell culture in polydimethylsiloxane devices

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ABSTRACT

Culture of cells using various microfluidic devices is becoming more common within experimental cell biology. At the same time, a technological radiation of microfluidic cell culture device designs is currently in progress. Ultimately, the utility of microfluidic cell culture will be determined by its capacity to permit new insights into cellular function. Especially insights that would otherwise be difficult or impossible to obtain with macroscopic cell culture in traditional polystyrene dishes, flasks or well-plates. Many decades of heuristic optimization have gone into perfecting conventional cell culture devices and protocols. In comparison, even for the most commonly used microfluidic cell culture devices, such as those fabricated from polydimethylsiloxane (PDMS), collective understanding of the differences in cellular behavior between microfluidic and macroscopic culture is still developing. Moving in vitro culture from macroscopic culture to PDMS based devices can come with unforeseen challenges. Changes in device material, surface coating, cell number per unit surface area or per unit media volume may all affect the outcome of otherwise standard protocols. In this review, we outline some of the advantages and challenges that may accompany a transition from macroscopic to microfluidic cell culture. We focus on decisive factors that distinguish macroscopic from microfluidic cell culture to encourage a reconsideration of how macroscopic cell culture principles might apply to microfluidic cell culture.

Contents

1. Introduction

Microfluidics refers to a set of technologies for the manipulation of small fluid volumes (μL, nL, pL), within artificially fabricated microsystems (Whitesides, 2006). Microfluidic systems enable

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generic and consistent miniaturization, integration, automation and parallelization of (bio-)chemical processes (Mark et al., 2010). The application of microfluidics to biology and medicine has lead to a diversity of new research directions (Melin and Quake, 2007; Yeo et al., 2011), some of which have had significant impact (Sackmann et al., 2014). Cell culture refers to the maintenance and growth of cells in a controlled laboratory environment. Such in vitro cell culture models are the mainstay of experimental cell biological research. Microfluidic cell culture attempts to develop devices and techniques for culturing, maintaining, analyzing and experimenting with cells in micro-scale volumes (Meyvantsson and Beebe, 2008).

Understanding the interplay between critical cell culture parameters and the microenvironmental conditions created by microfluidic devices will accelerate the development of microfluidic cell culture technology (Sackmann et al., 2014). Some important aspects of microfluidic cell culture systems have previously been reviewed, including the effect of surface modification on cellular behavior (Zhou et al., 2012), cell biology (Paguirigan and Beebe, 2008; Salieb-Beugelaar et al., 2010), cell culture models (Meyvantsson and Beebe, 2008), cellular analysis (Park and Shuler, 2003; Yeo et al., 2011), cellular microenvironment (Meyvantsson and Beebe, 2008; Young and Beebe, 2010), cell secretion (Huang et al., 2011), chemotaxis (Kim and Wu, 2012), apoptosis (Wlodkowic et al., 2011), vascular function (Wong and Chan, 2012), neuroscience in general (Soe et al., 2012), in particular neuron culture (Millet and Gillette, 2012) and development (Millet and Gillette, 2012), single cell resolution metabolomics (Rubakhin et al., 2011), population transcriptomics (Plessy et al., 2013), lab-on-chip platforms (Mark et al., 2010; Ni et al., 2009), large-scale integration and biological automation (Melin and Quake, 2007), micro total analysis systems (Kovarik et al., 2012), drug research (Wu et al., 2010), cellular separations (Bhagat et al., 2010), stem cell biology (Wu et al., 2011), system biology (Breslauer et al., 2006), bioreactors (Pasirayi et al., 2011), three dimensional cell culture (Haycock, 2011), tissue engineering (Inamdar and Borenstein, 2011), and efforts toward organs-on-chip (Huh et al., 2011).

Complementing the aforementioned reviews, the present review is aimed at researchers familiar with conventional/macroscopic cell culture, who are considering microfluidic cell culture for the first time. This review focuses on the practicalities of microfluidic cell culture and some advantages it may hold over macroscopic cell culture, but also the challenges that may accompany the culture of cells using a microfluidic device. Decisive factors are discussed that distinguish macroscopic from microfluidic cell culture. The overall aim is to give the reader a better understanding of the rewards and challenges that microfluidic cell culture can bring.

2. Advantages of microfluidic cell culture

Microfluidic cell culture has significant advantages over macroscopic culture, that is, culture in flasks, dishes and well-plates. Fig. 1 describes the most significant advantages and challenges when using macroscopic versus microfluidic cell culture. There is great flexibility in the design of microfluidic devices, which can be tailored to the needs of individual cell types and cellular co-cultures can be implemented on the same chip (Yeo et al., 2011). The advantages of microfluidic cell culture include the ability to more closely mimic a cell's natural microenvironment, for example by continuous perfusion culture or by creating chemical gradients, and to study low numbers of cells or single cells in high temporal and/or spatial resolution via automation, parallelization, on-chip analysis or direct coupling to downstream analytical chemistry

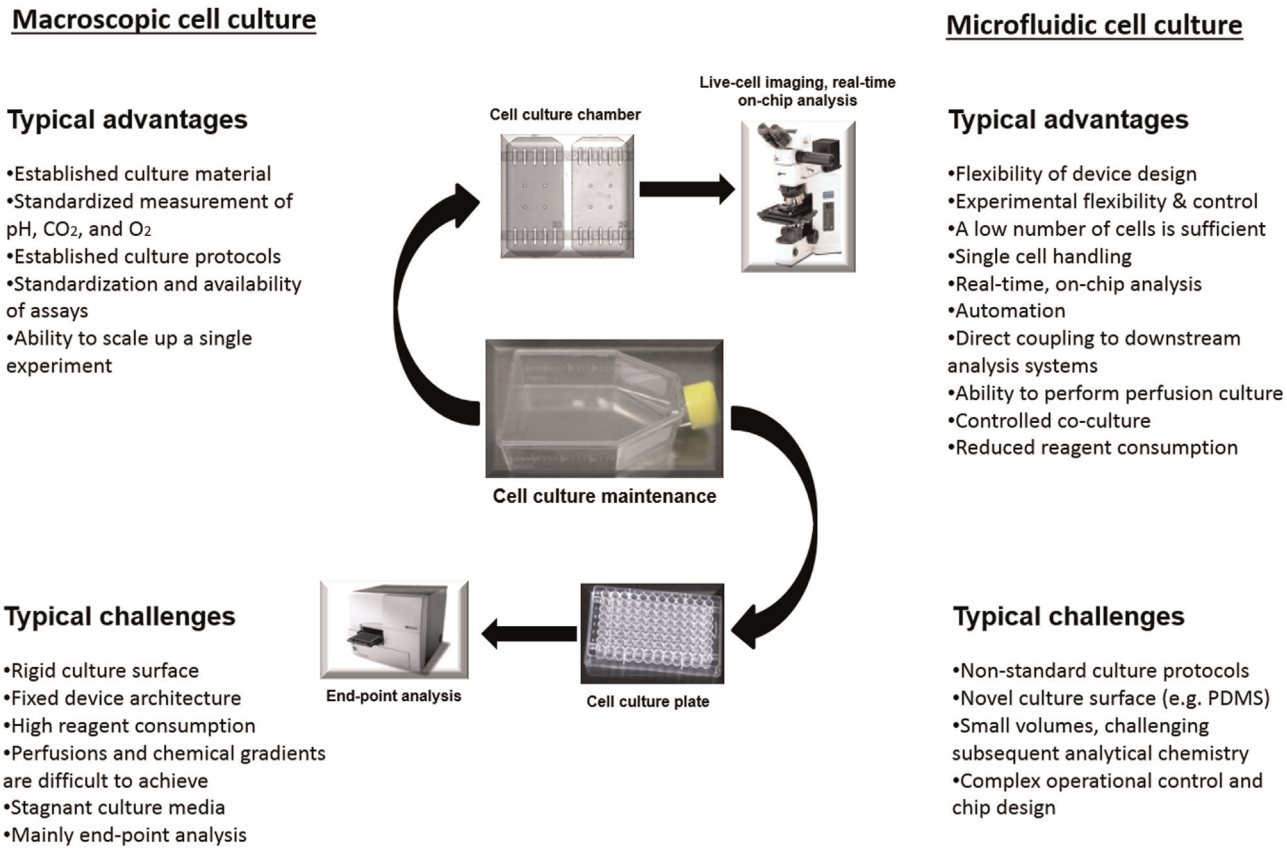

Fig. 1. Overview of advantages and challenges of both macroscopic and microfluidic cell culture.