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Review article

High-throughput screening approaches and combinatorial development of biomaterials using microfluidics

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ABSTRACT

From the first microfluidic devices used for analysis of single metabolic by-products to highly complex multicompartmental co-culture organ-on-chip platforms, efforts of many multidisciplinary teams around the world have been invested in overcoming the limitations of conventional research methods in the biomedical field. Close spatial and temporal control over fluids and physical parameters, integration of sensors for direct read-out as well as the possibility to increase throughput of screening through parallelization, multiplexing and automation are some of the advantages of microfluidic over conventional, 2D tissue culture *in vitro* systems. Moreover, small volumes and relatively small cell numbers used in experimental set-ups involving microfluidics, can potentially decrease research cost. On the other hand, these small volumes and numbers of cells also mean that many of the conventional molecular biology or biochemistry assays cannot be directly applied to experiments that are performed in microfluidic platforms. Development of different types of assays and evidence that such assays are indeed a suitable alternative to conventional ones is a step that needs to be taken in order to have microfluidics-based platforms fully adopted in biomedical research. In this review, rather than providing a comprehensive overview of the literature on microfluidics, we aim to discuss developments in the field of microfluidics that can aid advancement of biomedical research, with emphasis on the field of biomaterials. Three important topics will be discussed, being: screening, in particular high-throughput and combinatorial screening; mimicking of natural microenvironment ranging from 3D hydrogel-based cellular niches to organ-on-chip devices; and production of biomaterials with closely controlled properties. While important technical aspects of various platforms will be discussed, the focus is mainly on their applications, including the state-of-the-art, future perspectives and challenges.

Statement of Significance

Microfluidics, being a technology characterized by the engineered manipulation of fluids at the submillimeter scale, offers some interesting tools that can advance biomedical research and development. Screening platforms based on microfluidic technologies that allow high-throughput and combinatorial screening may lead to breakthrough discoveries not only in basic research but also relevant to clinical application. This is further strengthened by the fact that reliability of such screens may improve, since microfluidic systems allow close mimicking of physiological conditions. Finally, microfluidic systems are also very promising as micro factories of a new generation of natural or synthetic biomaterials and constructs, with finely controlled properties.

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1. Introduction

It is now becoming increasingly recognized that *in vitro* cell culture experimental set-ups in the conventional tissue culture plastics fall short in mimicking the natural *in vivo* microenvironment, which is considered one of the reasons for their limited predictive value. In addition to efforts required to overcome this issue, an increasing need exists for higher throughput of screening in the biomedical field, with the aim to accelerate the development of new and improved medical treatments against lower costs. In the field of pharmacology, high-throughput screening approaches were implemented relatively early, however, a large gap has been observed between the *in vitro* findings and the *in vivo* efficiency of the treatment, which is, for at least in a part, due to the use of over-simplistic conventional cell culture systems [1,2]. This gap becomes even larger when biomaterials are introduced into the system. Indeed, conventional cell culture platforms were developed to study cell–cell interactions and cell responses to soluble stimuli such as growth factors, antibiotics, small molecules, etc. Interestingly, such platforms were implemented into biomaterials research field without significant modifications. As a consequence, many have shown that results on cell–material interactions obtained in such simplistic systems are also poorly representative of the interactions that occur *in vivo* [3]. These issues with research systems having poor predictability will undoubtedly continue to exist, since state-of-the-art solutions for clinical problems, such as regenerative strategies for damaged and diseased organs and tissues, are gaining on complexity. Indeed, modern regenerative solutions often include combined contributions from biomaterials of different types, cell- and tissue constructs, growth factors, etc. On the other hand, our society is ageing, requiring the efficiency of discovery of clinical treatments to be maintained at a high level. To keep up with these scientific and societal developments, it is therefore evident that efforts need to be invested in the development of research systems that allow both faster and more reliable screening for biomedical applications.

In the past 10 years, the wealth of developments in the field of microfluidics has helped to establish a new set of standards in the study of basic biological phenomena. Microfluidics is defined as the science and technology of systems that process and manipulate small (10^{-9}–10^{-18} L) amounts of fluids by using channels with dimensions from tens to hundreds of micrometers [4]. Platforms based on microfluidics offer important advantages over classical *in vitro* cell culture systems such as close temporal and spatial control over fluids and physical parameters, integration of sensors for direct readout, and the possibility to increase throughput of screening by utilizing parallelization, multiplexing and automation. Furthermore, the micrometer scale makes microfluidic systems unique for having features in the range of a single cell size, which can be highly valuable in fundamental biological resarch, provided that also readouts are scaled down and their sensitivity reaches single cell resolution. Nevertheless, the validity of such assays, or the evidence that they are at least as reliable as conventional assays is needed for microfluidic platforms to be explored to the maximum extent. Alternatively to development of new assays, conventional analytical tools can be rendered applicable to microfluidic systems by means of customized interfacing [5].

Apart from the assays, the platforms as such, including the materials they are made from, and methods to produce them, need to prove their value for biomedical research. In early microfluidic systems for biomedical applications, rigid, inert materials such as silicon and glass, directly inherited from the field of microelectronics, reigned. However, current technology now allows the use of biopolymers that can be microfabricated to detail, tuned in their properties (e.g. stiffness, porosity, dielectric properties, hydrophilicity) by chemical changes, and biochemically decorated to better mimic the natural microenvironment [6]. These include photo- or heat-curable polymers such as SU-8 epoxy, polyimide photoresist, poly-dimethylsiloxane (PDMS) elastomer, as well as thermoplasts such as polymethylmethacrylate, polycarbonate, polystyrene, cyclic-olefin-copolymers and Teflon. Also the everlasting discussion between the PDMS-land engineers and polystyrenia kingdom biologists [7] has become further democratised, as a consequence of an exponentially increasing availability of complex materials that can be embedded in microfluidic devices, the on-demand delivery of smart hydrogels, and the nanometer-scale resolution printability of new scaffolding polymers and bioinorganics.

In this review, we aim to provide an overview of advances in the field of microfluidics that can aid biomedical research, with special emphasis on the field of biomaterials. We will do so by describing relevant examples of platforms that are developed with the aim of:

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