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Research review paper

Immunology on chip: Promises and opportunities

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ABSTRACT

Microfluidics has facilitated immunological studies by enhancing speed, efficiency and sensitivity of current analysis methods. It offers miniaturization of current laboratory equipment, and enables analysis of clinical samples without the need for sophisticated infrastructure. More importantly, microfluidics offers unique capabilities; including conducting multiple serial or parallel tasks as well as providing complex and precisely controlled environmental conditions that are not achievable using conventional laboratory equipment. Microfluidics is a promising technology for fundamental and applied immunological studies, allowing generation of high throughput, robust and portable platforms, opening a new area of automation in immunology.

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1. Introduction

Our knowledge of immunology has seen extraordinary advances over the past three decades, driving the creation of new therapeutics for human pathogenesis directed by the immune responses of our bodies (Medzhitov et al., 2011). Our immune system has evolved as a highly discriminatory defence mechanism to protect against potential invaders. Cells in the immune system form a complex network with other tissues and organs to defend our body. Immune cells are activated in response to pathogens or indeed any abnormalities within the system and begin sending signals to other cells. Many different signals have been identified; including the expression of different cytokines or protein markers, biochemical or mechanical interactions, cell-to-cell contact, or cell migration, which determine the progress of immune or inflammatory responses (Male et al., 2012). To study and understand such complex and subtle signalling mechanisms sophisticated and precise tools that can isolate each process at the microscale level are required.

Microfluidics, the science and technology of manipulating small scale of fluids (10^{-9} to 10^{-18} l) within microscale structures, has enabled powerful platforms for fundamental and applied biomedical research (El-Ali et al., 2006). In particular, microfluidics is a promising technology for miniaturization and parallelization of immuno-assays, while minimizing required sample volumes for precious and in some cases unique specimens. These characteristics are especially valuable for analysis of patient's samples with limited time, facilities and expertise. As such, microfluidic systems are ideal platforms for monitoring diseases in natural disaster affected areas or developing countries with resource-limited settings (Sun and Morgan, 2010; Toner and Irimia, 2005; Yager et al., 2006).

The most important advantage of microfluidic systems is their capability to process extremely low volumes of sample and reagents, which significantly reduces the cost of immunological assays and enables studying small and/or rare cell populations from clinical patients. More importantly, the flow remains laminar within the microfluidic systems, enabling the accurate control of flow variables such as velocity, pressure and temperature. This facilitates the analysis of immune responses under precisely controlled environmental conditions over target cells (Abhyankar et al., 2006; El-Ali et al., 2006; Vickers et al., 2012). Cells can be patterned in small clusters of a few or even single cells to obtain deep and uncluttered insight into the heterogeneity of the cell sample (Kim et al., 2009a). This enables studying the molecular machinery of individual cells with a precision that cannot be matched by conventional macroscopic counterparts (Sims and Allbritton, 2007).

Moreover, reducing the diffusion length leads to faster reaction times in microfluidic systems, enabling the dynamic analysis of immune cell responses to different and highly controlled stimuli (Faley et al., 2008). The increased surface-to-volume ratio of such systems also makes possible the rapid and sensitive detection of cells, nucleic acids or protein at very low concentrations that is essential early diagnosis of diseases (He and Herr, 2010; Khoshmanesh et al., 2011c).

Several microfluidic systems can be accommodated on a single chip and connected in customized configurations so as to realize the desired functionalities. They can be patterned either in parallel to increase the flow throughput of a particular sample or to conduct the same experiment under an array of environmental conditions; (Munce et al., 2004) or patterned in series to integrate multistep procedures such as sorting, immobilization, lysis and chemical stimulation of cells (Easley et al., 2006; Huang et al., 2006; Zare and Kim, 2010).

In this review, we describe the architecture of lab-on-a-chip systems to address a wide range of immunological studies and envision the trajectory that such systems will create for future research in immunology. We survey different microfluidic systems that have been introduced for cell based techniques, ranging from sorting, migration and cytotoxicity assays. We also present a collection of recent and topical microfabricated platforms for biochemical and molecular biology studies. Our objective is to identify systems that have recently been developed to replace the conventional bench-top infrastructures in immunology and show how, through the application of various technologies, highly integrated single chip biological assays of unprecedented capability are emerging. We believe that the microfluidic technology will become a key player in both fundamental research and applied immunology in the not too distant future.

2. The architecture of a future “immuno” lab-on-a-chip prototype system

The envisioned “immuno” lab-on-a-chip can be divided into three major parts including: cell; nucleic acid; and protein modules, as shown in Fig. 1.

The cell module is designed for sorting, trapping, stimulation, characterization and disintegration of cells. It is comprised of three functional elements: cell sorting and immobilization; cell analysis; and cell lysis units, which can be achieved by a variety of mechanisms and components (Fig. 1). These elements can be arranged in such a way that the cells can be directly applied to the “cell analysis” module or to the “cell sorter” module. Alternatively, the “nucleic acid” module is dedicated for trapping and analysis of target nucleic acids. It consists of purification, amplification and separation components. Finally, the “protein” module is dedicated for detection, trapping and characterization of target proteins. It consists of detection, purification, and separation components (Fig. 1).

The “immuno” lab-on-a-chip can serve either as an end-point system or as an interface with various off-chip technologies. For example, the immobilized cells can be interfaced with environmental scanning electron microscopy (ESEM) or total internal reflection fluorescent (TIRF) microscopy systems to conduct high/super resolution microscopy of cells. Alternatively, the separated proteins can be interfaced with electrospray ionization (ESI) or matrix assisted laser deposition ionization (MALDI) systems for mass spectroscopy of proteins and peptides.

3. On-chip manipulation of cells

3.1. Cell sorting and immobilization

The sorting of target immune cells is critical in many diagnostic, therapeutic and basic immunological studies. Samples of interest must often be isolated from a heterogeneous population of cells in blood or tissue. The standard methods available for cell sorting are often labour intensive and require multiple additional labelling steps to identify cells. Conventional cell sorting systems generally rely on continuous flow cytometry and are based on differential labelling of cellular populations. Flow cytometers use fluidic systems to deliver the stream of samples to the interrogation point and based on the labelling strategy can be divided into the fluorescent-activated cell sorter (FACS) or magnetic activated cell sorter (MACS) groups. In FACS, fluorescent conjugated antibodies are used for labelling the cells while in MACS, antibody conjugated magnetic beads are employed. Despite offering high

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