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Cell Analysis on Microfluidics

 Springer

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ISSN 2196-4475 ISSN 2196-4483 (electronic)
Integrated Analytical Systems
ISBN 978-981-10-5393-1 ISBN 978-981-10-5394-8 (eBook)
[https://doi.org/ 10.1007/978-981-10-5394-8](https://doi.org/10.1007/978-981-10-5394-8)

Library of Congress Control Number: 2017952915

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Printed on acid-free paper

This Springer imprint is published by Springer Nature

The registered company is Springer Nature Singapore Pte Ltd.

The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

It is an old Chinese saying that “proper tools for proper works.” To crack the mystery inside cells, special tool is demanded. At this moment, microfluidic chip represents an efficient and capable tool for cell analysis and biological study, and its rapid development is prompted by the great demands and wishes to one more step further the cellular biology research. The beginning of cellular biology studies started from the employment of petri dish as cell culture container. And until now, after repeated optimization and modification, dishes are still utilized in every biochemical laboratory. Typically, cell population at millions or tens of millions scale are cultured, stimulated, and harvested in one dish, and through these operations, researchers can carry out drug screening test and cellular components’ extraction from different cell batches. Depending on experiments consuming large cell population, results can be highly accurate and reliable, but also averaged. Imaging that cells of different phases in mitotic cycle and of different physiological situations and metabolism activities are equally averaged in signal calculation from one dish, individual behavior is completely wiped off. If we are going to look closer to cells, to reveal changes inside cell body and concern more about cell migration, division and apoptosis as well as cell–cell interaction by direct contact, a handy tool with cell manipulation and analysis capability can be indispensable. Under this circumstance, microfluidics was brought to the center of stage.

Unique advantages of microfluidics include less sample consumption, miniaturization and integration and function-oriented design. The invention of first microfluidic device can be dated back to 1970s, but not until 1990s did academic society start paying attention to this tiny chip. The bottleneck for its large-scale utilization is the expensive infrastructure and high cost to produce single piece of chip. After the successful fabrication of PDMS chip by soft lithography reported in late 1990s, PDMS-based microfluidic chip has spread to almost every laboratory inside university and academic institute. The most significant features of microfluidic chip are its microscale channel and flexible structure design. The dimension of microfluidic channel is on the same level as single cell, and therefore by flowing cell suspension inside microchannel and harnessing hydrodynamics in microregion, various manipulations such as cell transportation, isolation, sorting, and lysis are

realized. And different microfluidic techniques are invented according to different physics used. Besides, to realize cell components analysis, several types of detector can be coupled with microchip to implement online or offline analysis, such as noninvasive optical and electrochemical detection or invasive mass and electrophoresis.

As the continuous development of microfluidics and broadening of its application, more attention has been paid to employing microfluidic system to build up in vitro cell culture model or organ mimicry. Normally, complex cell culture model involves co-culture of multiple cell types, embedding cells into biocompatible hydrogels and adjusting interactions between cells and matrixes. Many works have been reported which made breakthroughs in improving bio-functionality of cell culture model, but fully recapitulation of organ function is still far away. In 13 chapters of this book, researchers and experts with deep insights in different fields present a detailed review and discussion over the design, formatting, application, and development of microfluidic chip related to cell biology research. Several techniques are being paid special attention, such as 3D cell culture, microfluidic droplet technique, and microfluidic chip-mass spectrometry interfaces.

The first part of this book concentrates on the history of invention and evolution of microfluidic chip and also the prospect of its future development. Chapter 1 (by Luyao Lin) summarizes from different aspects such as the choice of supporting materials, fabrication methods, functional units of microfluidic chips and also gives a brief discussion about its recent development. For chip fabrication, multiple 3D printing techniques that have been widely used in academic researches as well as industrial intention are introduced and compared to explore their further potential in chip formatting. Chapter 2 by Ziyi He highlights the advances in realizing cell culture, cell manipulation, cell stimulation, and cell analysis on chip. The highly flexible chip design permits implementation and integration of different functional units on the same chip, and makes microchip a powerful processing platform.

The second part of this book targets on several specific applications of microfluidic platform in cell biology researches. Chapter 3 by Qiushui Chen introduces two schematics to realize cell isolation, that is, physical and affinity-based cell isolation. Applications such as CTCs' capture and recognition and stem cells' purification are demonstrated. Chapter 4 by Linglu Yi depicts the critical factors influencing cell culture behaviors such as culture matrix and physical/chemical gradients. Nondestructive observation methods like optical and electrochemical detection are reviewed. In Chap. 5, Jinxin Dou introduces the application of microchip in studying cell migrating behavior and deciphering the influencing factors like chemotaxis, nutrients, and matrix rigidity. Ruizhi Ning of Chap. 6 presents the evolution of matrix materials for cell culture and highlights some novel biocompatible hydrogels with notable functions in establishing 3D cell culture environment and rehabilitating cell functionality. In Chap. 7, Junming Wang introduces the basic principle, different types of nozzle generators and compatible detectors of microfluidic droplet technology. Normally, optical observation through fluorescence labeling or simply bright field is the most convenient detecting method to determine the existence of target cells or biomarkers inside droplets, and this

noninvasive method allows continuous observation without interfering cell biological process. Other detectors such as mass spectrometry and electrochemical device are also included in this chapter. In Chap. 8, another unique advantage of microfluidics for cell analysis is well exemplified by Qiushi Huang. The content in this chapter involves the generation of single cells as well as the analysis of cellular components. Single cell sorting and lysis on microfluidics through controlling of hydrodynamics as well as other physical principles are described in detail. Chapter 9 by Ling Lin discusses the scheme of “From sample to data” by microchip online preparation and pretreatment with coupled mass detection, and varieties of chip-mass interfaces to achieve high throughput analysis are introduced.

The third part focuses on the construction of complex cell culture model on microfluidics and the on-chip analysis of cell metabolites as well as other cellular components. Chapter 10 by Jing Wu enumerates the latest design and realization of various chip functions about cell manipulation and analysis by taking advantage of physics phenomena such as electronic and magnetic field and surface acoustic wave, and their applications in genetic and protein analysis are introduced. In Chap. 11, Mingsha Jie describes the construction of “organ on chip” system for drug screening and evaluation. Duplication of real organ on chip includes not only the incorporation of multiple cell types, but also the implantation of complex cell–cell interactions. Chapter 12 by Xuexia Lin introduces the on-chip analysis methods of cell metabolites, among which self-designed fluorescent probes are specially emphasized. Aptamers with high degree of structure design freedom have been widely used for biomarker probes to achieve on-site and continuous fluorescence analysis, and therefore are an ideal candidate for microchip-based detection. In Chap. 13, Lin Zhou gives an overview about microorganism culture on chip and protocols of bacteria-related testing. There is no essential difference between culturing bacteria and eucaryote cells, but the rapid proliferation of bacteria makes it hardly a companion in direct co-culture with mammal cells.

Microfluidic platform has provided a powerful tool for microvolume sample analysis and cellular biology study, but there are still challenges waiting to be overcome. Highly remarked in novel device development, few of the microchip prototypes have been commercially transformed into established instruments, which may be due to its lack of competence comparing to well-validated conventional devices. But in recent years, this embarrassment has been alleviated and we have witnessed more and more large apparatus and equipment applying microchips as their core functional units. Some scholars may also question the accuracy and reliability of microchip in biological applications. It has to be admitted that cell-based microchip model is yet capable to replicate animal or clinical testing in drug screening or to verify a potential signal pathway among living organism. But as far as we consider, the structural mimicking on microchip is actually the first step on the road to build up more complex and functional in vitro organ models, and in some researches, on-chip method has made cell–cell interactions more detectable. Although chapters in this book only provide a brief review of microfluidics and limited collection of its applications on cell analysis, plenty of knowledge is included about almost every element to establish a microfluidic

platform. And we hope this book can be helpful to those ardent researchers and students who wish to know more, explore more, and achieve more in the fields of microchips and cellular biology. Also, I should gratefully thank the authors for their hard working and contributions to this book.

Beijing, China
June 2017

Jin-Ming Lin

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