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On-chip investigation of cell–drug interactions ☆

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ABSTRACT

Investigation of cell–drug interaction is of great importance in drug discovery but continues to pose significant challenges to develop robust, fast and high-throughput methods for pharmacologically profiling of potential drugs. Recently, cell chips have emerged as a promising technology for drug discovery/delivery, and their miniaturization and flow-through operation significantly reduce sample consumption while dramatically improving the throughput, reliability, resolution and sensitivity. Herein we review various types of miniaturized cell chips used in investigation of cell–drug interactions. The design and fabrication of cell chips including material selection, surface modification, cell trapping/patterning, concentration gradient generation and mimicking of in vivo environment are presented. Recent advances of on-chip investigations of cell–drug interactions, in particular the high-throughput screening, cell sorting, cytotoxicity testing, drug resistance analysis and pharmacological profiling are examined and discussed. It is expected that this survey can provide thoughtful basics and important applications of on-chip investigations of cell–drug interactions, thus greatly promoting research and development interests in this area.

Contents

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1. Introduction

Drug discovery is a complicated, time-consuming and costly endeavor, which continues to pose significant challenges. In recent years, rational use of combinatorial synthesis together with increased access to natural resources has enabled the rapid identification and synthesis of a vast amount of pharmaceutically valuable compounds [1]. Therefore, a robust and fast method to screen and validate potential drug candidates is urgently demanded for efficiency improvement, cycle and cost reduction of drug discovery [2,3]. In pharmaceutical research, cell culture based assays are increasingly exploited to bridge the gap between molecular level assays and animal tests, mainly because they can evaluate drug effects on cell proliferation, apoptosis and migration, and provide higher throughput than time-consuming animal experiments [3]. Currently, high-throughput screening techniques for automated and simultaneous analysis of thousands of pharmaceutical compounds on high density microtiter plates have become a gold standard to investigate cell–drug interactions. However, these methods encounter a number of limitations including long processing time, expensive equipment requirement, high reagent consumption and difficulty to mimic in vivo conditions [4]. Miniaturization of the entire system is a very promising way to overcome these limitations. In the past decade, tremendous advances in lab-on-a-chip (LOC) technology have made them as versatile tools progressively used in different stages throughout the drug discovery process [3].

1.1. The characteristics of miniaturized cell chips

The advancement of miniaturized cell chips brings a myriad of advantages that are inaccessible by conventional macroscale cell screening methods using microtiter plates. Prominently, the small dimensions of a typical cell chip greatly reduce cell/drug consumption, that is particularly important for rare cell analysis and cost reduction. Miniaturization leads to high surface area-to-volume (SAV) ratio, which facilitates heat transfer to achieve precise temperature control for healthy cell culture. Microfluidic cell chips operate in low-Reynolds (Re) number domain (e.g. $10 > Re > 0.001$), thus resulting in laminar fluid flow for a diffusion-dominated mass transport process to well resemble the in vivo condition. The small dimensions also greatly shorten mass and heat transport times to precisely regulate on-chip chemical processes for more efficient reaction kinetics and improved cell assay throughput. Another key feature of on-chip investigation is the integration of different functional units for cell–drug reaction, cell sorting and cell response detection to allow serial processing and analysis of various cell/drug samples. Massive parallelization of miniaturized functional units can be accomplished to achieve high throughput and multi-parametric analysis of drug induced cellular responses [2,3,5].

1.2. Classifications of cell chips

Cell chip is an emerging research field that includes two categories: microfluidic cell chips and non-fluidic cell chips such as cell microarrays [2].

1.2.1. Microfluidic cell chips

A microfluidic cell chip provides a set of fluidic operation units for miniaturization, integration, automation and parallelization of cell analysis [6]. It typically utilizes microchannels with several functional units such as micropumps and microvalves to transport drug compounds to target cells. The microchannel sizes are usually in the micrometer range, suitable for manipulating and culturing single cell or small cell clusters (Fig. 1) [2,7], while their network is able to perform multiple functions for cell pretreatment, transportation, analysis and sorting [8,9].

Recently, droplet-based microfluidics is becoming a novel paradigm for cell based high-throughput screening. It often uses a 2-phase system, in which each cell is compartmentalized in an aqueous microdroplet (1 pL to 10 nL) surrounded by an immiscible oil (Fig. 2). This technique is also known as “digital microfluidics”, whereby individual droplet can be generated, addressed, transported, stored, fused, split, sorted and analyzed [10–13]. Owning to its numerous advantages such as minimal cross-contamination, efficient mixing, high-throughput, low reagent consumption and flexible operation, droplet microfluidics presents an advanced route to investigate cell–drug interactions [14,15].

Despite the great potential of droplet microfluidics, a simple and effective method to produce compound droplets on-demand is still lacking. Wang et al. have applied electrohydrodynamic forces to form compound droplets with targeted coalescence of two water stream fronts in a microchannel [10]. Selective trapping and merging/fusion of droplets are also highly challenging. In practical applications, a droplet is often selectively trapped into a specific microwell and on-demand fused with another selected droplet, which has been realized by applying a controllable DC electric field [12]. On-demand droplet release from the microwell has been enabled by manipulating both dielectrophoretic (DEP) force and Columbic force. In such a way, on-demand trapping, fusion and release of droplet encapsulated single cells can be achieved on a single platform for high-throughput drug screening [13], which is feasible for further miniaturization with significant reduction of manufacturing expense.

1.2.2. Non-fluidic cell chips

Non-fluidic cell chips usually consist of solid supports where small volumes of cells can be displayed in defined locations, allowing multiplexed interrogation and analysis of living cells [1]. Two typical formats such as microwell cell chips and micropatterned cell arrays are displayed in Figs. 3 & 4.