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Microfluidics-Based Cell Manipulation and Analysis

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1. Introduction

Micro total analysis system, likewise named "lab on a chip", integrates sequentially analytical processes such as pre-treatment, separation, and detection of samples in a single microfluidic device. Microfluidics-based analysis systems have witnessed significant developments in applications of many research fields (e.g., chemistry, physics, and medicine) over the last two decades, becoming increasingly popular in recent years (Whitesides, 2006). Its popularity mainly stems from the advantages of microfluidics, including portability, low cost, easy operation, low consumption of samples and reagents, short reaction time, and function integration.

The integrated microfluidic devices perform rapid and reproducible measurements on small sample volumes while eliminating the need for labor-intensive and potentially error-prone laboratory manipulations. Of note, the microfluidic technique has begun to play an increasingly important role in research and discovery of cell biology and tissue engineering (El-Ali et al., 2006; Wang et al., 2009). Microfluidic technology enables the study of cell behaviour and activity from single- to multi-cellular organism level with precisely localised application of experimental conditions; this is almost unattainable with the use of common macroscopic tools (e.g., microplate and Petri dish). For example, the effect of laminar flow on the micron-scale enables spatial control of liquid composition, fast change of media and temperature, and single cell handling and analysis (Takayama et al., 2001). Meanwhile, microfluidic devices can realise biological experiments in a high-throughput way, while being based on the miniaturising macroscopic systems and taking advantage of massive parallel processing. Thus far, microfluidic applications have been involved in many experimental parts of cell manipulation and analysis, such as cell trapping/sorting, cell culture/co-culture, cytotoxicity, PCR, DNA sequencing, and gene analyses (Velve-Casquillas et al., 2010; Wlodkowic et al., 2009; Melin et al., 2007). Furthermore, a large number of novel microfluidic devices have been reported for cell research and tissue simulation in last 10 years (Ho et al., 2006; Huh et al., 2010; Sung et al., 2011).

According to various functional applications of microfluidic devices, we provide a discussion on general processes and overview of microfluidics-based cultivation of cells,

manipulation and analyses of plant cell fusion, cell-drug interactions, and cell-to-cell interactions. Monitoring of cell behaviour and precise control of cell microenvironments are intentionally mentioned as well.

2. Cell culture

Cell culture is the complex process by which cells are grown under controlled conditions. The cell culture methods used in this study is founded on over a century of scientific work. Although characterisation of microfluidic-based cell culture continues to develop, the multiple aspects of microfluidic environments have been understood and controlled. Microfluidic devices are suitable for biological applications, particularly on the cellular level, because of scale similarity between microchannels and cells. Scale of devices allows important factors (e.g., growth factors) to accumulate locally, forming a stable microenvironment for cell culture. Furthermore, the physical design of microfluidic devices affects the cell microenvironment of cultured cells. Design considerations and effective culture volume are useful for cellular control over the microenvironment in the microdevice. Engineering and applications of microfluidics, two- and three- dimensional culture of cells have been both described recently (Meyvantsson et al., 2008; Wu et al., 2010). In this section, we mainly present the diversified cultivation works to date on both mammalian cells, bacteria, and plant cells using microfluidic devices.

In the past 10 years, microfluidic-based applications of cell cultivation have ranged from many cell types from different tissues (e.g., epithelium and muscle) (Tourovskaia et al., 2005; Leclerc et al., 2006; Cimetta et al., 2009), organs (e.g., liver, lung, and kidney) (Zhang et al., 2008; Jang et al., 2010; Hoganson et al., 2011), even species (e.g., rat, cattle, human, and *Nicotiana tabacum*) (Ring et al., 2010; Taylor et al., 2005; Lee et al., 2006; Ko et al., 2006). Commonly, microfluidic culture modes of cells include the perfusion culture (continuous flow), half-perfusion culture (molecular diffusion with persistent supply of nutrients), and static culture (molecular diffusion). The perfusion culture is a popular application for the growth and proliferation of adherent cells. Low shear stress from microfluid in the channel leads to nearly no injury to the normal activities of these cell types.

Compared with static culture, the perfusion culture of cells cannot only keep the culture system sterile during the entire culture period. More importantly, however, it continuously provides a system for nutrient supply and waste removal, thus keeping the culture environment more stable. This contributes to steadier and more quantifiable extracellular conditions, which are particularly meaningful to the following cell-based research on microfluidic devices. Luke et al. presented a microfluidic cell culture array for long-term culture and monitoring of human carcinoma cells (Hela cells) at 37 ^{o}C (Hung et al., 2005). Major functions of the device include reagent introduction, cell growth, cell passage, and real-time optical analysis based on the perfusion model. The cell culture array can offer a platform for a wide range of assays, with applications in bioinformatics and quantitative cell biology. Yu et al. (Zhang et al., 2009) developed a multichannel three-dimensional microfluidic cell culture system (multi-channel 3D-μFCCS) with compartmentalised microenvironments. To this end, the multi-channel 3D-mFCCS was designed for culturing different 3D cellular aggregates simultaneously to mimic multiple organs in the body. Four human cell types (C3A, A549, HK-2, and HPA cells) were chosen to represent the liver, lung, kidney, and adipose tissue, respectively. Cellular functions were optimised by supplementing the common medium with growth factors. Such a multi-channel 3D-mFCCS

may be potentially used to supplement or even replace animal models in drug screening. However, certain highly environment-sensitive cell types such as neuron are always maintained and cultured in the static or half-perfusion microenvironment of the devices (Hosmane et al., 2010).

Meanwhile, diffusion is likewise used for the suspension culture of cells such as bacteria (*Escherichia coli*) and plant cells (tobacco mesophyll protoplasts) (Ko et al., 2006; Sun et al., 2011), which requires greater control in the devices due to non-physical dependence.

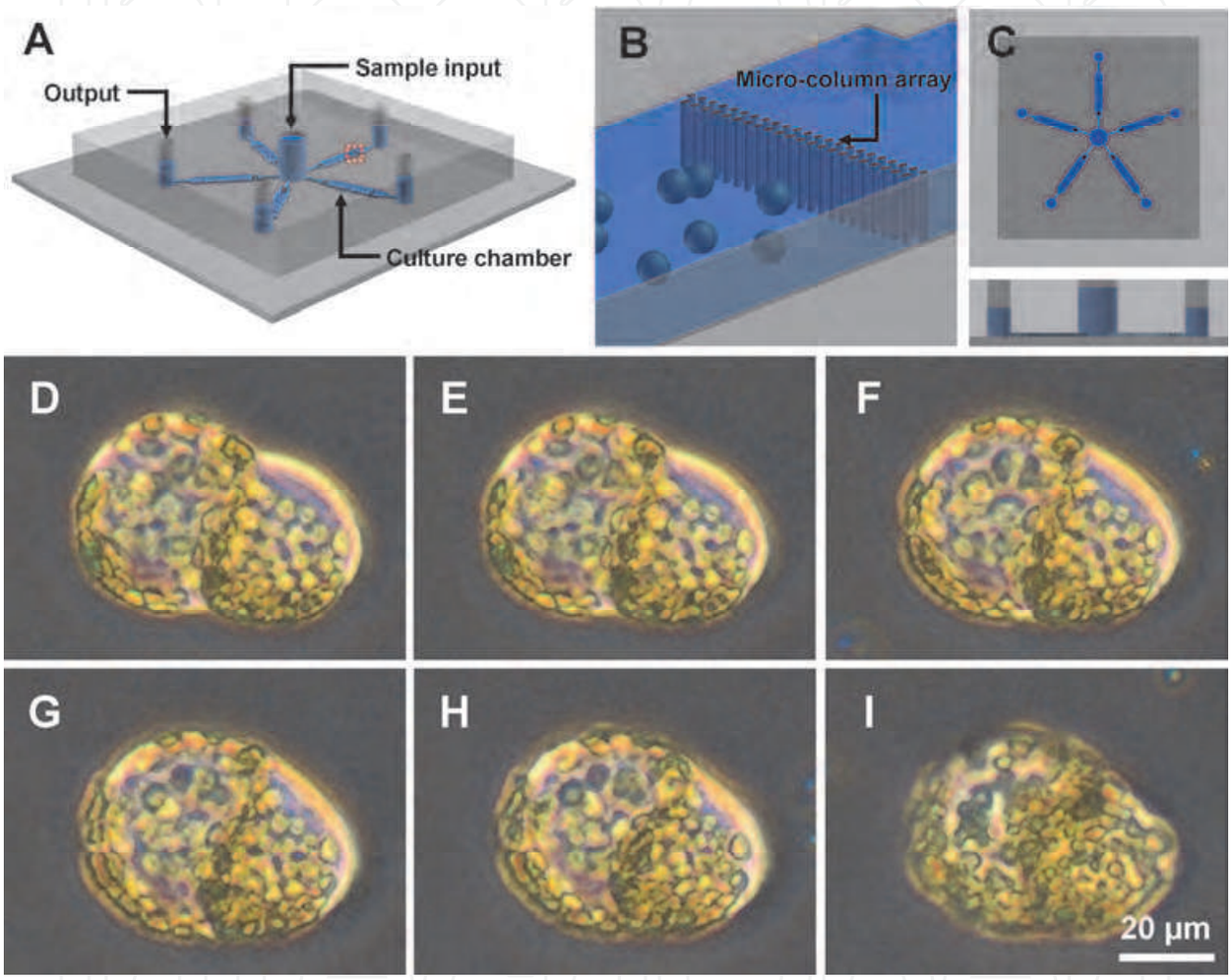

Fig. 1. Configuration and function of the microfluidic device. A. Schematic representation of the device with five culture chambers arranged in a pentagonal array and applied for the parallel culture of protoplasts. A center sample input was designed for the introduction of various liquids, including protoplast suspension, rinsing solution, culture medium, and dye. The square in the red dotted line corresponds to B. Double micro-column lines in each chamber were designed to promote trapping of protoplasts while the seeding process (B). The gap between micro-columns was 20 μm. C. Plan (up) and elevation (down) of the microfluidic device. Hydrostatic pressure was used to realize material transportation using a small volume difference. D-I. Chemical fusion of the tobacco mesophyll protoplasts was performed in the microfluidic device using polyethylene glycol (PEG). The time when the two protoplasts contacted is considered as the start of fusion (i.e., 0 s) (D), followed by 10 s (E), 30 s (F), 50 s (G), 80 s (H), and 190 s (I).

Application of microfluidics in the field of plant cell biology is close to nil. Recent microfluidic advances in plant cell research contain the preliminary cultivation of protoplasts, the relationship between high air permeability of polydimethylsiloxane (PDMS) and protoplasts, and fusion manipulation of protoplasts as well (Ju et al., 2006; Wu et al., 2010). The protoplasts became vulnerable in the in vitro environments as they were separated from the protection of cell walls. The highly spatiotemporal control of microenvironment is necessary to maintain the viability and activities of protoplasts during primary culture. Based on the optimal supplication of nutrients and design of microfluidic devices, growth up to formation of visible cell mass was achieved recently in the microfluidic cultivation of protoplasts (Wu et al., 2010). On-chip protoplast culture showed that percentage of the first division may be improved to as high as 85.6% in five days.

3. Plant cell fusion

As typical genetic manipulation in plant cell engineering, cell fusion (i.e., protoplast fusion) has been used for various purposes, including generation of hybrids and reprogramming of somatic cells. Cell fusion, generally called somatic cell hybridisation, is an excellent tool for breeding and genetic analysis of engineered plants (Ogle et al., 2005). To expand microfluidic application in plant cell manipulation, Wang et al. presented a conceptual attempt at protoplast fusion in the microfluidic device (Figure 1) (Wu et al., 2010). Tobacco mesophyll protoplast fusion was performed through polyethyleneglycol (PEG)-induced fusion.

The results revealed that adjacent protoplasts came into close contact with one another, and membrane of the contacted protoplasts fused. Therefore, a connection was formed between the two cytoplasms. Components of both contacted protoplasts, especially the chloroplasts, mixed and combined with one another. Finally, the two protoplasts formed a fusion product with an irregular shape, which was different from the common spherical shape. The possible reason for deformation can be the spatially mechanical response of the fusion body in the microfluidic device because of increased volume. Total duration of this fusion in the microfluidic device merely took approximately 3–5 min, achieving a fusion rate of 28.8%. This result is similar to the conventional fusion in a macroscale culture environment.

4. Cell-to-chemical stimuli interactions

In vitro cell-based assays have been regarded as a promising substitute to in vivo animal testing in research on cell and chemical materials (e.g., drugs). Ideally, a cell culture model faithful to in vivo behaviour offers significant advantages in saving time and cost in cell-based research. Microfluidics, which has been demonstrated to provide a biologically relevant and well-defined cellular microenvironment, is needed to maintain the phenotypic properties of tested cells; this is necessary to investigate faithfully and precisely the cellular response to specific drug compounds or conditions. The inherent cellular microenvironments mimicked in a microfluidic system suggested that research on cell-to-chemical stimuli interactions can be performed in a microscale, high throughput, and physiologically meaningful manner. Most microfluidic cell culture systems used in this research exploit a perfusion cell culture format in which medium flows are not only used to feed cultured cells continuously but likewise to provide additional functionalities such as generating gradients of drug concentrations (Wu et al., 2010; van Midwoud et al., 2010;

Sugiura et al., 2008), creating a specific physical microenvironment (e.g., shear stress or interstitial fluid flow) and constructing a circulatory system to mimic in vivo conditions better.

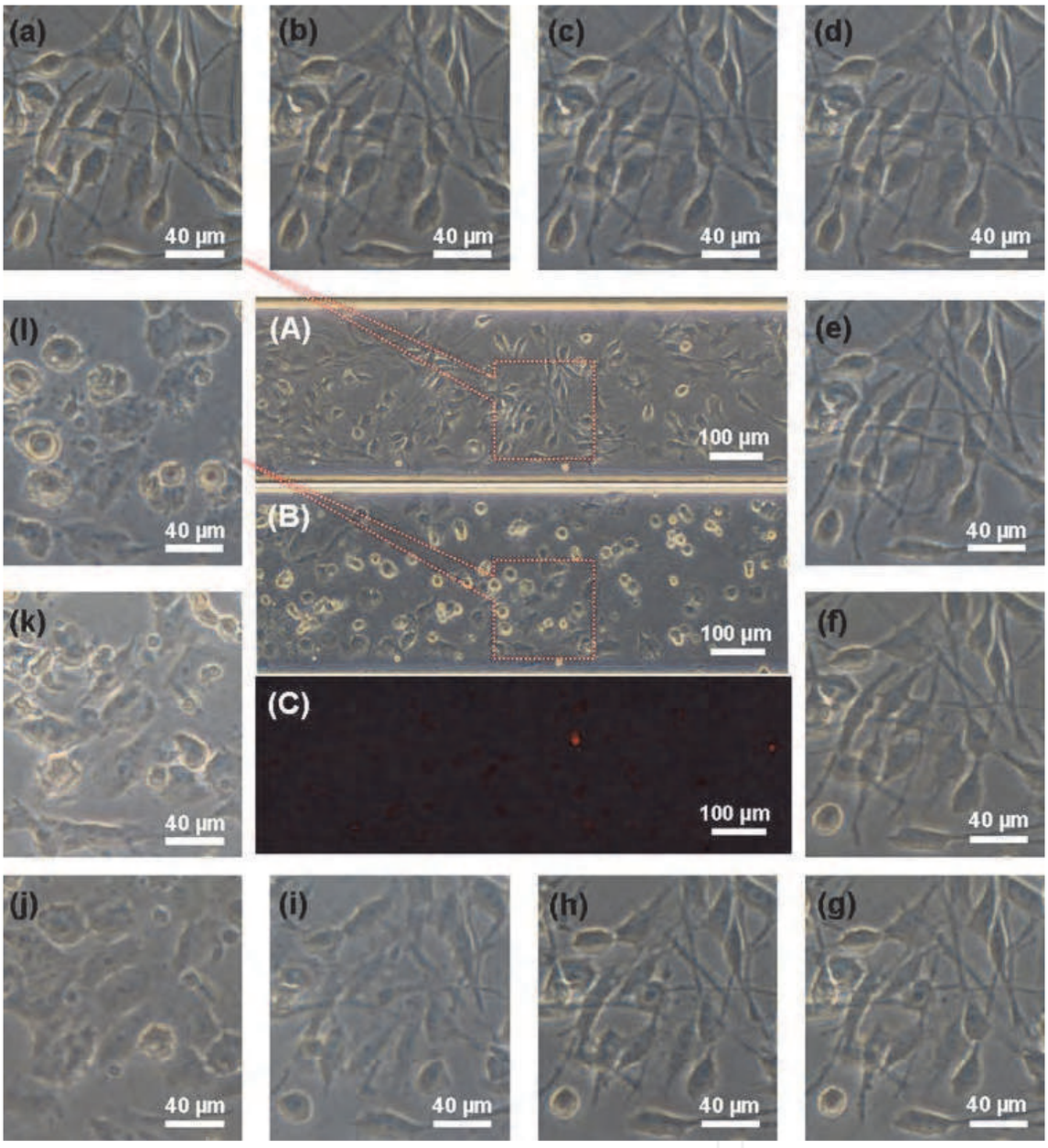

Fig. 2. Cellular responses of rat C6 glioma cells to colchicine treatment (0.5 μg/ml): (A) Rat C6 glioma cells cultured for 2 days; (B) Rat C6 glioma cells treated with colchicine for 60 h; (C) Fluorescence image of PI-stained rat C6 glioma cells for cell viability assessment after colchicine treatment for 60 h; a–l cellular responses of rat C6 glioma cells after 0.5 μg/ml colchicine introduction (0, 15, 30, 60, 90, 140, 180, 210, 420 min, 24 h, 48 h, and 60 h).

Wang et al. developed a glioma-related microfluidic method for studying brain tumour therapy (Liu et al., 2010). Glioma cells were cultured successfully for up to seven days in a microfluidic device, and cellular responses to the anticancer drug (colchicine) were monitored in real time (Figure 2), followed by the analyses of cell viability by using

propidium iodide (PI) staining. Temporal changes in cell morphology at various concentrations of colchicine were recorded using an inverted microscope and charged coupled device (CCD) imaging. According to results, the number of injured/dead cancer cells and morphological changes increased relative to the drug's concentration and treatment frequency. The achievement is helpful in developing microfluidic device applications for future research on brain tumour, conducting cytotoxicity research in a biomimetic microenvironment, developing glioma-related anticancer drugs, and developing glial cell-based biosensors for glioma detection.

5. Cell-microenvironmental interactions

Extracellular environment provides important and necessary conditions for cell proliferation, differentiation, metabolism, and functional activities; it determines cell behaviour (e.g., cell polarisation and migration) and fate (i.e., survival or death). Actually, cell-microenvironmental interactions (cell-to-matrix, cell-to-cell, and cell-to-soluble factors) are known to occur in many physiological and patho-physiological processes such as embryological development, wound healing, tumour invasion, and metastasis (Gurtner et al., 2008; Bhowmick et al., 2004; Bullock et al., 2001). Due to their specific occurrence and progress, a spatio-temporal controlled investigation in vitro and the understanding of these valuable and interesting biological cues are of great importance to cell biology and histology.

Microfluidics is becoming a promising platform for the study of cell-microenvironmental interactions, mainly because of its excellent performance in precise control, monitoring, and manipulating cells and their microenvironments in vitro in a spatial and temporal manner. Recently, several microfluidic systems have shown good real-time manipulation of cell culture and cellular responses to simultaneous stimulation of soluble cues (Gómez-Sjöberg et al., 2007; Park et al., 2010), and an excellent microfluidic system for studying mammalian cells in 3D microenvironments has presented one of its possible utilities in the study of cell-cell communication (Lii et al., 2008). Ingenious design and real-time manipulation of microfluidic system play an important role for versatile studies of cell-microenvironmental interactions, especially the serial and dynamic procedures of these studies. Furthermore, it is notable that perfusion cell cultures may hamper cell-to-cell communication through intrinsic and extrinsic growth factors because of the continuous washing away of these biomolecules.

Wang et al. presented an integrated microfluidic system for dynamic study of cell-microenvironmental interactions (Figure 3) (Liu et al., 2010). They demonstrated its precise spatio-temporal control in the flow direction and multisite staying of fluids by groups of monolithic microfabricated valves through digital operation, in addition to the regulated communication between two loci based on real-time microenvironment transition. Using this system, a series of functional manipulations, including specific delivery, addressable surface treatment, positional cell loading, and co-culture were performed quickly and efficiently for biological applications. Sequentially, they performed the potential utility of this system in research on dynamic microenvironmental influence to cells using a patho-physiological interaction during cancer initiation and progression. The results exhibit the passive role but collaborative response of NIH 3T3 fibroblasts to the soluble signals from hepatocellular carcinoma cells, as well as the variable behaviours of carcinoma cells under different environmental stimulations. This system can facilitate the in vitro investigation of cell-microenvironmental interactions occurring in numerous biological and pathogenic processes.

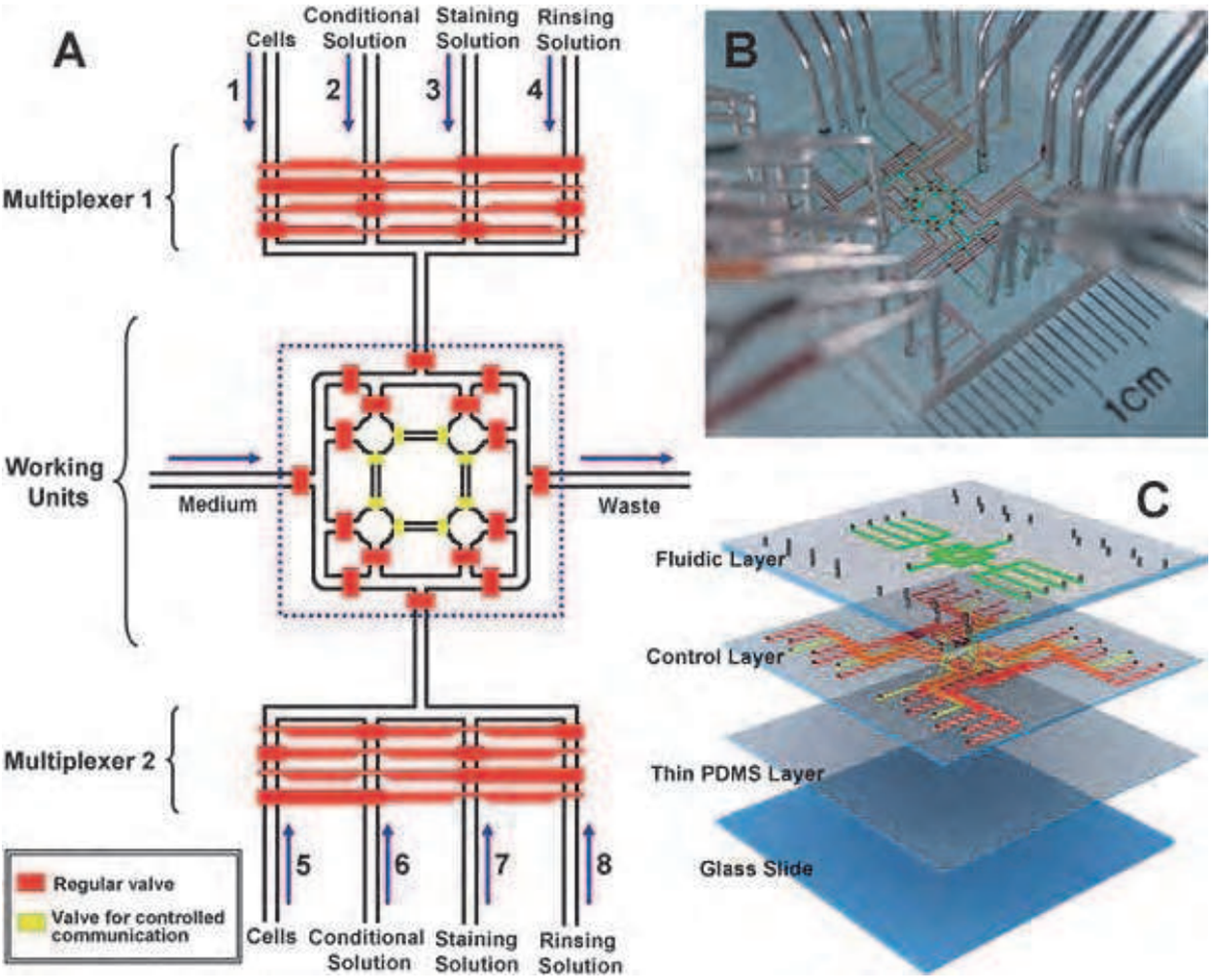

Fig. 3. Configuration of the integrated microfluidic system. (A) Schematic representation of the functional circuit used for cell-microenvironmental interactions. The responsibilities of different valves are illustrated by their colors: red for regular valves (for isolation) and yellow valves (for communication of the adjacent chambers). (B) Optical image of the actual device. The various channels were loaded with food dyes to help visualize the different components of the microfluidic chip; the colors correspond to those in (A), with green indicating the fluidic channels. (C) Composition of the microfluidic device (four layers sequentially from top to bottom, including the fluidic layer, control layer, thin PDMS layer, and glass slide).

6. Conclusions

After a decade of development, microfluidics has demonstrated its capability to serve as a powerful tool for cell manipulation and analysis. Successful applications of microfluidics for cell-based assay – including cell lysis chip, cell culture chip, electroporation chip, biochemical sensing chip, and whole cell sensing chip – have revolutionised the way we approach the subject. Single cell-based microfluidic devices for various excellent experiments will be the future direction of this research area. Meanwhile, diversified development can be the major strategy for the application of microfluidics to life science in the next two decades.

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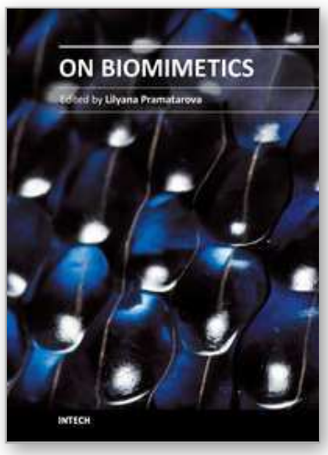

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