Device for Sorting of Biological Cells

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ABSTRACT

Cells differ by type not only in shape but also in mechanical, electrical, and magnetic properties. Cells can be sorted using these properties. Based on each principle, devices for cell sorting have been designed. This is a technology applied to cell diagnosis and tissue formation promotion. In this research, the advantages and disadvantages of devices have been compared and the direction of future research was discussed. This technology is expected to be applied to the elucidation of cell properties, disease diagnosis, and regenerative medicine.

Keywords: Cell Sorting, Dielectrophoresis, Microfilter and Microchannel.

1. INTRODUCTION

Cell sorting technology is applied to many devices in the biomedical field. Target cells are sorted from a suspension based on the physical and chemical properties of the cells.

Sorting technology is used in regenerative medicine, analysis, etc. It can be applied to the detection of cancer cells.

In this study, previous research on cell sorting [1] was categorized and the direction of future research was discussed. In cell sorting technology, a target sample is obtained from multiple cells.

This technology is expected to be applied to the elucidation of cell properties, disease diagnosis, and regenerative medicine.

2. METHODS FOR SORTING

Magnetic Field

Using an externally applied magnetic field, cells containing magnetic substances are manipulated [2]. This technology is minimally invasive and does not affect the function of cells *in vivo* [3].

Centrifuge

This technique is often used in experiments in biology and biochemistry. It is based on the principle of separating components with different densities using centrifugal force [4]. Since centrifugal force is used, the rotational speed of the centrifuge is important [5]. Because it is minimally invasive, cells can be sorted without damaging them. Large amounts of samples can be processed simultaneously.

Shear Flow Field

The shear flow field technique is utilized in microchannels. Cells are manipulated using the shear force exerted on them by moving fluids in a flow field at different speeds. This is used for the label free cell separation technique [6].

Laser

Laser produces high-intensity light at a specific wavelength. This property is used to select cells and microparticles [7]. This device requires light source equipment. In the case of identification methods using fluorescent substances, there is a possibility of damaging cells.

Filter

Filters are used as part of microfluidic devices [8, 9]. Sorts particles by passing through or blocking particles of a specific size. If clogging occurs, efficiency decreases.

Dielectrophoresis

Dielectrophoresis manipulates cells using an asymmetric electric field [10]. This will be applied as particulate separation technology [11].

It is also attracting attention as a method for separating and sorting cells. Since cells can be manipulated without contact, the risk of damaging cells is low. Previous research has confirmed that cells are not damaged by electric fields [12].

3. CELL SORTING EXAMPLES

Magnetic Field

Cell separation using a magnetic field allows for non-contact operation [13-17]. Physical damage to cells can be minimized. However, it is necessary to attach magnetic beads or magnetic fluids to the cells. It may affect the state and function of cells.

Microchannel

It is efficient because cells are sorted as the fluid moves. In microchannels, gravity, flow around a small cylinder, inertial flow, and viscoelasticity are used. A method appropriate to the characteristics of the cells is selected. Sorting conditions are difficult to generalize.

By taking advantage of concentration gradients and surface effects, highly sensitive reactions and detection on a fine scale are possible. Fractionation can be performed with a small amount of reagent. Because the device is operated in a small flow path, it is necessary to be handled in a contamination-free environment.

Table 1: Study with microchannel; *w* (width), *h* (height)

Factor	Condition	Threshold	Cell	Ref
Gravity	36 µL/min	Density	Viability of yeast cell	[18]
Gravity	0.29 µL/min	Density	Red & white blood cell	[19]
Flow around micro-pillars	200 µL/min	Size	MG-63	[20]
Flow around micro-pillars	50 µL/min	Size	Escherichia coli	[21]
Lift by fLow	70 µL/min, Aspect ratio= 0.33	Density	EO771, PY230	[22]
Flow	23 µL/min	Size and stiffness	White blood cell	[23]
Visco-elasticity	w = 125 µm, h = 40 µm; 197 µL/min	Size	Fluorescent microsphere	[24]

Microfilter
Passage of particles is restricted by size and shape.This is often used in simple methods. Cells may be damaged due to physical contact with the filter surface.

Table 2: Study with microfilter; CTC (Circulating Tumor Cells), CAML (macrophage-like cells).

Shape	Size	Cell	Ref
Hole	15 µm, 10 µm	CTC	[25]
Hole	d = 7 µm, t = 10 µm	CTC, CAML	[26]
Slit	w = 10 µm, t = 25 µm	CTC	[27]
Hole	d = 10 µm,	CTC	[28]

Dielectrophoresis
Cell separation using dielectrophoresis allows for non-contact and long-distance operation. It is possible to separate cells while minimizing physical damage to cells. It is a method that can be used for various types of cells.

Table 3: Study with dielectrophoresis; 3T3 (embryonic fibroblasts), HFF (Human Foreskin Fibroblasts), MC (fibroblast), RBC (red blood cell), MDCK (epithelial cells from kidney), HRBC (horse red blood cells), hMSC (Mesenchymal Stem Cell), MDA-MB-231 (human breast adenocarcinoma).

Electrode	Volt, Frequency	Cell	Ref
Muti-layer 3D	5 V-20 V, 50 kHz-300 kHz	3T3, 293FT, HFF	[29]
29 micro-cylinders	6 Vp-p-20 Vp-p, 10 kHz-1.1 MHz	RBC, T-cell, U937-MC	[30]
Comb-shaped Ni	40 Vp-p-50 Vp-p, 1 kHz	3-2H3, HeLa, MDCK	[31]
Ti. Parallel	50 V-300 V. 1 kHz	3-2H3, HRBC	[32]
Comb-shaped Au	15 V. 3 MHz	hMSC, osteoblast	[33]
Au, 3D	50~100 Vp-p. 1 kHz-1 MHz	Polystyrene beads, MDA-MB-231, neuron cells	[34]
L-shape	60-80 V	8-4 µm particle	[35]

Photolithography technology, sputtering technology [36, 37], electron beam lithography technology [38, 39], and inkjet printing technology [40, 41] are used to manufacture electrodes.

4. DISCUSSION

Each method has advantages and disadvantages. The future direction of cell sorting devices has been discussed. In some cases, sorting cells is difficult. There are cases where the characteristics of each cell cannot be utilized in sorting techniques. There are cases where the differences in characteristics between cells are extremely small. Designing a sorting device that can be applied to a wide variety of cells is difficult, and is a future challenge.

Separation methods using microfilters often involve physical contact between cells and filters. Considering the use of cells after fractionation, it is necessary to select a method that is as least invasive as possible.

It is necessary to bind magnetic beads or magnetic fluids to cells in a magnetic field. There is a need to consider the compatibility and stability of magnetic materials with cells.

In the following, cell separation methods using dielectrophoresis and microchannels are focused on. Non-invasive cell separation is possible using these two methods. In dielectrophoresis, cells are passed along with a fluid and separated by an electric field. It is possible to combine a microchannel on the dielectrophoresis channel. By utilizing multiple characteristics of the cells to be sorted, it is possible to develop an efficient and highly selective sorting device. The challenge is to develop smaller, more portable devices and automated separation systems.

A sorting technique that can be applied to multiple different cells is expected. Applications are expected not only in medicine but also in environmental monitoring. Improvements in stability and efficiency are required. Elucidation of the mechanism of cell sorting will lead to new technologies. It is desirable to develop cell sorting techniques that have less impact on cells.

5. CONCLUSION

In this study, conventional research regarding devices for cell sorting was categorized. Future research developments were considered based on current issues. This technology is expected to be applied to the elucidation of cell properties, disease diagnosis, and regenerative medicine.

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