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REVIEW

Research Progress on Microfluidic Chip of Cell Separation Based on Dielectrophoresis

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Abstract: Cell separation technology is an important means for cell sorting and cell-population purification. It is the current international hotspot in biochemical analysis which is widely applied in many fields such as biology, medicine, agriculture, and environment. This review introduces the development status of cell separation using microfluidic chip based on dielectrophoresis (DEP). It expounds the working principle of DEP and the key factors that impact the DEP of cell separation such as cellular size, electrode shapes and signals. Finally, it forecasts the future development trend of cell separation using microfluidic chip based on DEP.

Key Words: Dielectrophoresis; Cell separation; Microfluidic chip; Electrodes; Review

1 Introduction

Cell separation is an important method of purification process[1], and is of great importance in biological research. Many research fields based on cell separation technology, such as clinical diagnosis, environmental monitoring, food processing and pharmaceutical industry, which require highly sensitive detection of target cells and pure processing[2–5]. Currently, the electromagnetic operations of biological particles in suspension are a hot research topic in the field of biological analysis, and cell separation is the most important one.

Traditional cell separation methods can be divided into two types[6]. The first ones, including centrifugation and gravity deposition methods, depend on the size and gravity of cell. This type of separation method has some disadvantages, such as low precision, separation for a long time, complicated to operate and a larger effect on cell activity. The second ones, including the electrophoretic separation and magnetic separation etc., usually require the cell to be charged or modifying cell with magnetic materials, and then are respected to be separated with the help of magnetic field or electric field. Attachments on the cell produced in the preprocessing of separation are difficult to be removed and greatly influence the cell activity. In addition, the complex operations can only be completed by some professional equipment such as hydrocyclone and flow cytometry instrument, which make it expensive and inaccessible.

Dielectrophoresis (DEP)[7] is derived from electrophoresis technique, but does not need the particles to be charged. It can drive the electrically neutral particles to move in DC or AC electric field by polarizing the particles non-uniformly. DEP technique, since was introduced into biological and chemical fields by Pohl in 1978[8] and applied to cell separation and manipulation, has attracted the attention of the researchers from all over the world[9]. Compared with traditional electrophoresis method, this technology has many advantages [10–12]. For example, it doesn't need to label the antibody, which can avoid changing the biological properties of cell in the process of separation. AC electric field with low intensity is non-destructive to the cell. A large number of researches have shown that it would not influence the cell growth and

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division. DEP technique, with its flexibility and simplicity, can be combined with some other techniques to achieve the best effect of cell separation.

In recent years, based on the theories of dielectric electrophoresis and the rapid development in manufacture technology of microfluidic chip, cell separation on microfluidic chip combined with DEP becomes a research hotspot[13–16]. Liquid flow can be easily controlled and small sample volume is needed on this experimental system, which is not only limited to cell, but also mineral particles with micron scale[17], polystyrene microspheres[18], droplet[19], bacteria[20,21] and yeast[22], even virus[23], nanoparticles, DNA[24], and carbon nanotubes[25,26], etc.

Research progress on microfluidic chip of cell separation based on DEP was introduced in this review. In addition, some key factors that influence DEP were summarized, and different types of microfluidic chip were classified.

2 Theory of dielectrophoresis for cell separation

Oriented movement of charged particles in electric field was called electrophoresis and that of electrically neutral particles (dielectric) in non-uniform field was called the dielectric electrophoresis (DEP)[27]. Electrically neutral particles such as cells were polarized in non-uniform electric field and form electric dipoles which could be moved by the electric field[28,29].

If particles are more polarized than electrolyte solution, the force along the field strength on the particles is bigger than the solution. Then, the electrically neutral particles would gather at region with the maximum electric field. This phenomenon is called positive DEP, and the force is called positive DEP force. The opposite phenomenon called negative DEP and nDEP force[30].

Spherical particles or cells suspended in fluid medium and exposed in a non-uniform alternating electric field would subject to the DEP force (F_{DEP}) according to the dipole mode[31,32] which can be expressed as follows:

$$F_{DEP} = 2\pi\varepsilon_0\varepsilon_f r^3 \nabla E_{rms}^2 \operatorname{Re} K^*(\omega) \quad (1)$$

$$K^*(\omega) = \frac{\varepsilon_p^* - \varepsilon_f^*}{\varepsilon_p^* + 2\varepsilon_f^*} \quad (2)$$

$$\varepsilon_f^* = \varepsilon_f - j\frac{\sigma_f}{\omega} \quad (3)$$

$$\varepsilon_p^* = \varepsilon_p - j\frac{\sigma_p}{\omega} \quad (4)$$

Where, ε_0 is the vacuum dielectric constant, and r is the radius, ε_p, σ_p are, the relative dielectric constant and the conductivity of the particles, respectively. ε_f, σ_f are the relative dielectric constant and the conductivity of the medium. ω is the angular frequency of external electric field signal, and E_{rms} is root mean square of electric field strength. The direction of the DEP force depends on the real part of $K^*(\omega)$ which is called Clausius-Mossotti factor and will be referred to CM factor and represented by $f_{\mathrm{CM}}(\omega)$, hereinafter. If $\mathrm{Re}[K^*(\omega)] > 0$, particles in the non-uniform electric field would be attracted from region with low field strength to that with high electric field, which is positive dielectrophoresis (pDEP). Conversely, if $\mathrm{Re}[K^*(\omega)] < 0$, particles would be excluded from region with high electric field strength to low one, which is negative dielectrophoresis (nDEP). Equation (1) is no longer applicable if the phase change, under this condition, calculation of the DEP force becomes complex because it is related to the imaginary part of $K^*(\omega)$, called travelling wave DEP (twDEP)[33,34].

The separation of cells was realized by the different movement rate and direction under the DEP force, so CM factor-frequency map[35] was important to cell separation. Generally, there are two different methods can be used to realized the cell separation. Firstly, suitable frequency was chosen to make the different cells subject to DEPs with different direction. Secondly, all of the cells suffer the same DEP but with different magnitude.

3 Different types of microfluidic chip for cell separation

Based on the Eq.(1), apart from the properties of cells and the medium, the DEP mainly depends on the electric field gradient, which makes the shape of the electrodes become a critical factor for the success of the cell separation [36,37]. In addition, the frequency and the buffer solution also can be optimized to maximize the DEP.

3.1 Microfluidic chip used DEP for separation based on cellular size

The sizes of the cells range from several microns to several hundreds of micrometers. The DEP force in non-uniform electric field is proportional to the cube of cell radius r. Therefore, cell with different size can be separated by the same DEP with different magnitude. The following will introduce different kinds of microfluidic chip based on cellular size.

3.1.1 Microfluidic chip of cell separation based on dielectrophoretic Field-flow-fractionation (FFF)

The flow in the pipe is laminar flow. Wang *et al*[38,39] reported a cell separation method based on dielectrophoretic field-flow- fractionation (DEP-FFF) as shown in Fig.1. Arrays of interdigitated electrodes were microfabricated on the bottom of a thin and rectangular chamber. The height of the cell location depends on the equilibrium of DEP and sedimentation (F_{sed}) forces. Therefore, the cells with different size would locate at different height and subject to different flow rate, thus, ravel to different outlets finally.

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