Introduction

Dielectrophoresis (abbreviated DEP) is an electrical phenomenon of induced movement of particles (such as cells) in an electrical field, whose magnitude is dependent upon the electrophysiology of the cells; a spectrum or “fingerprint” of signals can provide information about both the cell membrane and the cytoplasm. The phenomenon has been known of for decades, but only recently has the technology been developed to allow accurate assessment of cells in seconds rather than hours, at low cost, and without the need for chemical labeling. Furthermore, the same technology can be used for cell sorting based on the same electrophysiological traces.

DEPtech (a joint venture between staff at the University of Surrey, England, and life sciences technology distributor Labtech International) have developed the only DEP cell analyzer currently on the market. Launched at the beginning of 2014, prototype devices have been used in labs across the world – from the UK to US to Norway – with the specific aim of investigating cellular changes due to stem cell differentiation. Notable results include the first demonstration that DEP can be used as a biomarker for neural stem cell differentiation, where fluorescent labels can only identify actual differentiation rather than differentiation potential (in collaboration with University of California Irvine). A recent study with the Gade institute in Bergen, Norway showed that membrane electrical properties can indicate the presence of tumorigenicity in stem cells. In both of these cases, it is the electrical properties of the cell membrane, both composition and morphology, which discriminate between cells. The effects show a “sliding scale” of proportionality between the degree of variable (the tumorigenicity, or the likelihood of forming neurons or astrocytes) that can be exploited when analyzing harvests of iPS cells.

Papers from other DEP groups have confirmed differences in cells such as these, but DEPtech has the commercialised technology with the launch of the 3DEP cell analyser.

3DEP Technology

The physical principle on which DEP is based is straightforward; capacitive materials (those that form dipoles in an electric field) will interact with a spatially non-uniform electric field (i.e. one where a gradient in the field is present), because the forces on the two poles are different – the pole at the higher point of the gradient will dominate, and the direction of force will be “up” or “down” the gradient depending on the orientation of the dipole (Figure 1). That orientation is dependent on both the properties of the object generating the dipole (in this case, a cell) and the frequency of the applied field; analyzing the response of the object at different frequencies allows its properties to be elucidated (Figure 2). Furthermore, for complex particles such as cells, the response is a combination of the contribution of both the cytoplasm and the membrane, which can be determined independently.

Figure 1. Particle undergoing dielectrophoresis

Figure 2. Cells in non-uniform fields will be attracted to regions of high electric field (positive DEP, above left) or repelled from them (negative DEP, above right) according to their properties and the frequency of the field. Determining the way in which this response changes produces a spectrum (points, below) that can be analyzed to determine the properties of the particle
The 3DEP system uses a patented chip design which is low-cost, simple to use and allows the analysis of thousands of cells simultaneously. Using a novel approach to chip design, the cells are analysed in “wells”, about a millimeter in both height and diameter, around the perimeter of which are gold-plated electrodes. These draw cells towards or away from the cell wall; the motion of the cells is tracked and a measurement taken (Figure 3).

The chip reader device, called the 3DEP, can analyse 20 wells simultaneously, allowing rapid analysis; whereas typical DEP measurements in the past would take 2-3 hours, the 3DEP takes only ten seconds.

Furthermore, the approach can be applied to cell separation. Where a frequency exists at which one cell type in a mixture experiences a DEP force attracting it to the electrodes (called positive DEP) whilst the other is repelled from the electrodes (negative DEP), it is possible to separate them on a chip. We have developed a new range of chips to do this, which can currently separate cells in the ml/min regime, but which could be scaled to meet your applications. Yet another advantage of DEP analysis and separation is that because the technique is entirely label-free and completely non-invasive, the analyzed cells are unharmed by the process and can be recovered after analysis for continued use.

**Applications**

Unlike molecular marker methods that respond to chemical changes in the cell, DEP is sensitive to physical changes; this can be in the form of cytoplasm ionic content and composition, membrane potential, membrane conductivity, morphology and roughness, size and shape. Many of these changes precede those identified by fluorescent labels by some significant margin.

**Apoptosis** - One of the first cell changes in apoptosis is a small efflux of water from the cytoplasm, which alters the cytoplasmic ion concentration and which in turn can be identified by DEP within 30 minutes of drug treatment, whereas common methods such Annexin V can take up to 24h to identify equivalent effects.

**Stem cell differentiation** - One key finding is in the study of both human and murine neural stem cells, the likelihood of a cell differentiating into a neuron (rather than an astrocyte) is inversely proportional to its membrane capacitance producing a shift in the DEP spectrum (see figure 4). This was found to replicate across species, between cells at different passage number, and between human and mouse embryonic stem cells of different ages.

![Figure 3. A schematic showing how cells move in DEP-Wells. Cell movement can be tracked by image analysis for cell characterization, or cells can be separated by retaining one population by positive DEP](image)

![Figure 4. Differences in DEP spectra of neuron-fated and astrocyte-fated stem cell populations, identifiable substantially in advance of other physical or chemical markers](image)

Similar work has also been conducted on investigations of differences in the electrical properties of different populations of stem cells within bone marrow samples.
Cancer cells and cancer detection
In cancer cells the degree of tumorgenicity (a stem cell-like characteristic of metastatic cells to form new tumours) also correlates to changes in membrane morphology, indicating that tumourgenicity in stem cells should also be detectable by this method.

Non-stem cell based studies have highlighted differences between normal and cancerous cell lines and primary samples -so much so that the 3DEP is currently in clinical trials for oral cancer detection.

Papers

Apoptosis

Stem Cell

Cancer

Interested in analysing your cells using 3DEP?
Want to arrange a test of the system in your lab, with your cells and applications?
Contact Labtech International Ltd on sales@labtech.com or call +44 (0) 1825 744 690

For more information about 3DEP visit our website www.labtech.com and/or contact us via email sales@labtech.com