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Process optimization and biocompatibility of cell carriers suitable for automated magnetic manipulation

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ABSTRACT

There is increasing demand for automated cell reprogramming in the fields of cell biology, biotechnology and the biomedical sciences. Microfluidic-based platforms that provide unattended manipulation of adherent cells promise to be an appropriate basis for cell manipulation. In this study we developed a magnetically driven cell carrier to serve as a vehicle within an in vitro environment. To elucidate the impact of the carrier on cells, biocompatibility was estimated using the human adenocarcinoma cell line Caco-2. Besides evaluation of the quality of the magnetic carriers by field emission scanning electron microscopy, the rate of adherence, proliferation and differentiation of Caco-2 cells grown on the carriers was quantified. Moreover, the morphology of the cells was monitored by immunofluorescent staining. Early generations of the cell carrier suffered from release of cytotoxic nickel from the magnetic cushion. Biocompatibility was achieved by complete encapsulation of the nickel bulk within galvanic gold. The insulation process had to be developed stepwise and was controlled by parallel monitoring of the cell viability. The final carrier generation proved to be a proper support for cell manipulation, allowing proliferation of Caco-2 cells equal to that on glass or polystyrene as a reference for up to 10 days. Functional differentiation was enhanced by more than 30% compared with the reference. A flat, ferromagnetic and fully biocompatible carrier for cell manipulation was developed for application in microfluidic systems. Beyond that, this study offers advice for the development of magnetic cell carriers and the estimation of their biocompatibility.

1. Introduction

In nature the stimuli for the differentiation of cells are recognized at the surface and transmitted to the nucleus via intracellular signalling pathways. Currently advances in induced differentiation have been made either by addition of soluble factors such as growth factors [1–3], determination factors [4,5], and vitamins [6] or by surface-mediated cell differentiation via immobilization of adhesion molecules [7] or matrix molecules [8]. Additionally, cells have been manipulated by genetic programming [9].

Recently in vitro cell cultivation and differentiation have been recognized as fundamental tools for progress in medicine and pharmaceutics, especially considering that defined differentiation of cells and targeted manipulation of the destiny of an individual cell are becoming more and more feasible. However, cell culture requires work-intensive handling, restricting its routine applicability. Efforts have been made to automate screening assays in the microplate format [10] and to monitor cellular changes by measuring physical values such as voltage [11] and impedance [12].

Addressing the increasing demand for miniaturization, microfluidic systems provide a well-established basis to scale down analytical devices for biological applications. Moreover, microfluidics is a promising technology in cell-based screening as the benefits include reduced reagent consumption and thus lower cost [13]. Furthermore, its feasibility for real time monitoring of erythrocytes has been demonstrated and applied for the nanoparticle-driven manipulation of cells [14]. The techniques to manipulate cells within a microfluidic system include dielectrophoresis, standing wave ultrasound and magnetism using either particles as vehicles

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