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Nanofiber topography and sustained biochemical signaling enhance human mesenchymal stem cell neural commitment

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ABSTRACT

Stem cells hold great promise in enhancing nerve regeneration. In particular, human mesenchymal stem cells (MSC) represent a clinically viable cell source due in part to their abundance and accessibility. Unfortunately, current methods to direct the fate of stem cells remains largely limited to biochemical-based approaches on two-dimensional substrates with restricted efficacies. Here we have evaluated a scaffold-based approach to directing stem cell differentiation. We demonstrate the combined effects of nanofiber topography and controlled drug release on enhancing MSC neural commitment. By encapsulating up to 0.3 wt.% retinoic acid (RA) within aligned poly(ε-caprolactone) (PCL) nanofibers (average diameter ~270 nm, AF750), sustained released of RA was obtained for at least 14 days (~60% released). Compared with tissue culture polystyrene (TCPS), the nanofiber topography arising from plain PCL nanofibers significantly up-regulated the expressions of neural markers, Tuj-1, MAP2, GalC and RIP at the mRNA and protein levels. Combined with sustained drug availability, more significant changes in cell morphology and enhancement of neural marker expression were observed. In particular, scaffold-based controlled delivery of RA enhanced MAP2 and RIP expression compared with bolus delivery despite lower amounts of drug (>8 times lower). The generally higher expression of the mature neuronal marker MAP2 compared with glial markers at the mRNA and protein levels suggested an enhanced potential of MSC neuronal differentiation. In addition, positive staining for synaptophysin was detected only in cells cultured on aligned scaffolds in the presence of RA. Taken together, the results highlight the advantage of the scaffold-based approach in enhancing the potential of MSC neuronal differentiation and demonstrated the importance of the drug delivery approach in directing cell fate. Such biomimicking drug-encapsulating scaffolds may permit subsequent direct cell transplantation and provide guidance cues to control the fate of endogenously recruited stem cells.

1. Introduction

Stem cells hold tremendous potential in the treatment of nerve injuries and neural diseases [1–3]. Amongst the various cell types explored, mesenchymal stem cells (MSC) probably hold the greatest promise for translational applications, due in part to their greater abundance and easier accessibility compared with neural stem cells and embryonic stem cells. However, neural differentiation in MSC remains ambiguous [4–6]. While multiple studies have demonstrated the potential of MSC to differentiate into progenitor cells expressing neural specific markers [7,8] and the ability of these cells to enhance nerve regeneration in vivo [2,9], there remains a search for a deeper understanding of the factors that govern MSC differentiation into non-mesenchymal lineages.

Furthermore, regardless of the choice of stem cell type, being able to specifically direct stem cell fate remains a limitation to the widespread clinical application of stem cell therapy. One of the major obstacles lies in the recapitulation of the stem cell niche. While studies thus far have demonstrated some degree of success in mimicking the biochemical signals required during stem cell differentiation [7,8], other works have suggested the critical and synergistic roles played by the extracellular matrix (ECM). In particular, substrate compliance and architecture signaling are important in directing cell fate [10,11]. Therefore, being able to combine several microenvironmental signals within a single scaffold construct would be attractive in achieving the ideal artificial stem cell niche design.

Nanofiber matrices mimic the architecture and size scale of the natural ECM. Compared with two-dimensional (2-D) substrates, nanofiber constructs provide more three-dimensional (3-D) biomimicking topographical signals to seeded cells and result in more

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