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Compressive elasticity of three-dimensional nanofiber matrix directs mesenchymal stem cell differentiation to vascular cells with endothelial or smooth muscle cell markers

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ABSTRACT

The importance of mesenchymal stem cells (MSC) in vascular regeneration is becoming increasingly recognized. However, few in vitro studies have been performed to identify the effects of environmental elasticity on the differentiation of MSC into vascular cell types. Electrospinning and photopolymerization techniques were used to fabricate a three-dimensional (3-D) polyethylene glycol dimethacrylate nanofiber hydrogel matrix with tunable elasticity for use as a cellular substrate. Compression testing demonstrated that the elastic modulus of the hydrated 3-D matrices ranged from 2 to 15 kPa, similar to the in vivo elasticity of the intima basement membrane and media layer. MSC seeded on rigid matrices (8–15 kPa) showed an increase in cell area compared with those seeded on soft matrices (2–5 kPa). Furthermore, the matrix elasticity guided the cells to express different vascular-specific phenotypes with high differentiation efficiency. Around 95% of MSC seeded on the 3-D matrices with an elasticity of 3 kPa showed Flk-1 endothelial markers within 24 h, while only 20% of MSC seeded on the matrices with elasticity >8 kPa demonstrated Flk-1 marker. In contrast, ~80% of MSC seeded on 3-D matrices with elasticity >8 kPa demonstrated smooth muscle α-actin marker within 24 h, while fewer than 10% of MSC seeded on 3-D matrices with elasticity <5 kPa showed α-actin markers. The ability to control MSC differentiation into either endothelial or smooth muscle-like cells based purely on the local elasticity of the substrate could be a powerful tool for vascular tissue regeneration.

1. Introduction

Vascular diseases affect one in three Americans [1]. In 40% of cases, the treatment requires surgical replacement of a diseased or dysfunctional blood vessel with a vascular graft. Synthetic vascular grafts cannot always match the efficacy of healthy vessels, leading to short-term or long-term graft failures, including thrombosis or stenosis. These failures may be partly prevented by the development of a robust endothelial layer using the patient's cells along the inner wall of the graft. Recent developments in vascular tissue engineering have shown exciting potential for using both endothelial cells (EC) and smooth muscle cells (SMC) on a degradable scaffold to regenerate blood vessels [1,2]. However, obtaining a sufficient number of vascular cells is difficult, as it requires invasive surgery on the patient or donor, and these cells have a limited expansion capability in vitro [1]. Mesenchymal stem cells (MSC) are an alternative cell source recently employed in vascular graft or tissue engineering [3,4]. MSC are multipotent and thromboresistant, can be easily obtained through a bone marrow biopsy from a patient or a compatible donor, have a large expansion capability, given proper environments in vitro, and thus are increasingly explored for regenerative medicine [5]. Studies in the last decade have demonstrated that MSC differentiation and spreading can be controlled by local mechanical elasticity using a polyacrylamide gel with varied modulus as a two-dimensional (2-D) cell substrate [6]. It has been demonstrated that the gels that replicated the modulus of neural, muscle and bone tissue directed the differentiation of MSC towards neural, myogenic and osteogenic cells, respectively [7]. Using the local substrate elasticity to control MSC differentiation and activity is an elegant approach to achieving spatial control of cell behavior.

In contrast to the 2-D cell culture employed by most of these studies, the in vivo extracellular matrix provides a cellular microenvironment characterized by a three-dimensional (3-D) nanofiber

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